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FOREWORD

THE American medical profession may well feel proud of its medical journals. As one turns the printed pages which present the day-by-day advance of scientific medicine, one realizes why the character of medical thought is on so high a plane.

It is the constant advance of medicine which makes the glory of our profession. The three great learned professions have been theology, law, and medicine. The church too often substitutes man-made creeds for the teachings of the Sermon on the Mount. The law is necessarily one generation behind the social life of the people, as legal opinions are to a large extent concerned with established precedents, the yesterdays of life. Medicine constantly advances, and tomorrow is the great day.

The large majority of the members of the medical profession are hard-working, intelligent, earnest men, eager to give their patients the benefit of the latest scientific knowledge. In the process of the physician's education after graduation from medical school, medical books, clinical trips, and attendance at medical meetings play important parts, but above all, familiarity with the contents of current medical journals is essential. To the physician, patients represent medicine in practice, books on medicine represent stabilized medical opinion, and medical journals, the very breath he breathes, represent medicine in the making.

America has many medical journals which collectively give a viewpoint of medicine as a whole. Of these publications, the *Journal of the American Medical Association*, with about 100,000 subscribers, is outstanding—the greatest achievement in the history of medical journalism. The special fields of medical science are covered by many excellent journals which appeal to those physicians who are practicing the specialties. Surgeons having access to the splendid surgical journals already in publication may for the moment wonder whether there is a good reason for such a surgical publication as that proposed by the editorial board of SURGERY, now making its initial appearance.

If one divides the 3,000 miles of territory of the United States between the Pacific and the Atlantic into three major sections, it is ap-

parent that the Mississippi Valley is the largest area, geographically if not in numbers of population. In this great tract of country between the Rockies and the Alleghenies, SURGERY will become, to some extent at least, the organ of clinical surgery of the Middle West; and yet it will not be local in any respect, but an organ of the world's surgical thought. This journal, brought out by a well-known medical publishing house, will receive the ethical supervision which is characteristic of American medical journals of the highest class.

SURGERY has two editors. Dr. Alton Ochsner, the distinguished American surgeon, Head of the Department of Surgery at Tulane University, New Orleans, has won for himself an international reputation. Dr. Owen H. Wangensteen, Professor of Surgery and Head of the Department of Surgery of the Medical School of the University of Minnesota, has made splendid contributions, not only to clinical surgery, but to scientific investigation.

Associated with Dr. Ochsner and Dr. Wangensteen in SURGERY are two associate editors. Dr. Alfred Blalock, Associate Professor of Surgery at Vanderbilt University, is one of the leaders of surgical thought in the South. Dr. William F. Rienhoff, Jr., Associate Professor of Surgery at Johns Hopkins Medical School, has made splendid contributions to surgical progress, and is a worthy representative of the Hopkins school of advanced medical thought.

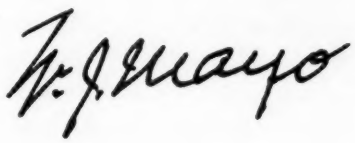
In addition to the distinguished editors and associate editors, SURGERY is fortunate in its Advisory Council of nine members, its Editorial Board of sixteen members, and its Committee on Publications of forty members, an extraordinary roster of able and distinguished members of the surgical profession of America.

It is pleasing that the editors of SURGERY are representative of the southern and the northern extremes of the great Mississippi Valley. With expanding traffic on the Mississippi River and its tributaries as the result of the growing exchange of commodities by boat and barge with Mexico and Central and South America, through the port of New Orleans, which is second only to that of New York in shipping, the Middle West will be brought increasingly into contact with tropical diseases of various types, as the Atlantic seaboard and the Pacific seaboard already have been exposed to these diseases. We know that tropical diseases are being brought farther and farther north as their bacterial and insect carriers are becoming acclimatized to the conditions of the North Temperate Zone. The study of the cause and treatment of these diseases must constitute henceforth a part of the medical curriculum. Mexico and Central and South America have much of scientific value to give to the medical profession of the United States. The Latin American surgeons of the earlier day were trained largely in the French schools, and contributed greatly to the advancement of surgery. One who visits the medical schools, clinics,

and hospitals of Latin America will be interested and impressed, as I have been, by the high character of these physicians and surgeons and their contributions to medical and surgical thought. We of the profession in the United States will welcome increasing cooperation with our learned confreres of Mexico and Central and South America.

When this war-torn world has settled down again, shall we not find that American money, American inventions, and American scientific instruments of various kinds have added greatly to Europe's ability to provide for herself economically? Japan at the present time apparently is master of the Orient. But the countries to the south of us are an open field, affording a vast opportunity for mutual usefulness, economically as well as educationally and scientifically. SURGERY can do much to advance the exchange not only of surgical knowledge but also of social and economic thought and practice which may be of the greatest reciprocal value.

The idea of SURGERY appeals to my brother, Dr. Charles H. Mayo, and me, to our spirit and imagination. We know of the great numbers of young surgeons who will be interested in this venture and will profit by it. Speaking for ourselves, when we have written medical articles, we have profited more than the readers, because in the preparation we have been obliged to look up many scientific matters with which otherwise we might have been unfamiliar. The new journal of surgery will fulfill a useful purpose. It will stimulate the younger men to write, and in the writing they, even more than their confreres, will gain; above all, it will disseminate scientific surgical knowledge which will aid in the care of the sick.



EDITORIAL ANNOUNCEMENT

THE growth of medical knowledge during the time which parallels the development of the new science of bacteriology has been unprecedented in the annals of medical history. The employment of a new approach to old problems succeeded overnight in differentiating with precise methods what centuries of speculation and plodding effort had failed to do. Medical journals multiplied to record the successive discoveries and conquests. New and unfamiliar specialties of practice sprang into being to assail disease in the interphases between medicine, chemistry, and physics.

The number of recognized specialties in the broad field of medicine has become so large as to impose a great task on anyone who should attempt to enumerate them all. The problem of relating the gains in skill and knowledge of any of these groups to the others has obviously become intricate and difficult. A method which will serve to coordinate more intimately these newly gained increments of enlightenment and bring their advantages to the practical man of medicine is highly desirable.

There can be no longer a sharp distinction between that which is medical and that which is surgical. The borders between medicine and surgery are not fixed, but are constantly changing. There is a continual striving to find means of treating surgically diseases which are refractory to medical management; at the same time an uninterrupted search is always in progress for conservative agents which may adequately replace satisfactory, but more energetic, operative methods. The sole anxiety of surgery is no longer concerned with the treatment of wounds. Surgery has emerged from a handicraft to occupy an important position in the treatment of disease. Its influence has been felt in every branch of medical science and practice.

Indispensable as the surgeon has become to society and his medical confreres, even more dependent is he upon the life-giving spirit of close association with fellow workers in the broad domain of medicine. Surgeons are not long the best company for one another. There is only enough sustenance in a purely surgical fare for subsistence; for growth, a free admixture of the vitalizing ingredients of other forces of medicine is essential. "Man shall not live by bread alone," and surgeons cannot thrive on the lone products of their own efforts.

In essence, SURGERY is an attempt at integrating more effectually the many interphase activities of the surgeon. The need has become great for a more intimate correlation between the increasingly divergent medical and surgical specialties. No group can suffer isolation long without

revealing unmistakable signs of want. The superiority of the medical assembly in which different points of view are brought to bear upon a subject of common interest is becoming more generally recognized. Witness the developments which have recently occurred in the province of thoracic surgery through the fusion of various branches of specialized medical knowledge. Obviously, it is a far simpler task to effect such a correlation for one province of surgery; yet, so far as is practicable, an endeavor to achieve the same purpose in the wider scope of general surgery appears meritorious. A large number of individuals of diverse training and interests have lent their talent and willing hands to this enterprise to help secure that end.

The columns of SURGERY invite concise papers of new matter relating to the broad field of surgery, its specialties and interphases with other provinces of medical practice and science. To authors, SURGERY will aim to assure early publication of original matter; to readers, it will strive to bring a digest of what is new and best in surgery and its frontiers.

The importance of the stimulus which splendid surgical journals of this and other countries have lent sound practice is inestimable. The pages of SURGERY will be dedicated to the ideal which they typify—the improvement and advance of surgery.

Alton Ochsner *Owen H. Wangensteen*

Original Communications

THE SURGICAL TREATMENT OF SCLERODERMA

Rationale of Sympathectomy and Parathyroidectomy (Based Upon Experimental Investigations and a Clinical Study of 26 Personal Cases)

Rene Leriche, Adolphe Jung, Strasbourg, France, and Michael De Bakey,* New Orleans, La.

(From the Surgical Clinic A, Director: Professor Rene Leriche, Strasbourg, France)

THE ideal and trend of modern surgery may be characterized by the continuous search for a more ratiocinative comprehension of the less obvious alterations in physiologic functions consequent to the more apparent anatomicopathologic processes. This is readily evinced by the ever-increasing number of previously considered nonsurgical diseases, which in the past decade have entered the widening realms of surgical endeavor. A recent characteristic example of this form of progress is the considerable attention which scleroderma has received from surgeons throughout the world. Until relatively recently this disease has been considered a purely dermatologic condition gladly relegated to that specialty.

Scleroderma is the term applied to the syndrome characterized by sclerosis, induration, and pigmentation of the skin which may be localized or generalized and frequently associated with asthenia, digestive disturbances, arthritis, muscle atrophy, and other symptoms depending upon the gravity and degree of involvement. The profound and voluminous literature already amassed in a comparatively short period of time is clearly indicative of the existing confusion and bewilderment concerning the etiology and pathogenesis of this disease. It would be inexpedient as well as inopportune to attempt here a detailed review of this phase of the subject. Even at the risk of being invidious, we prefer to confine this presentation to a discussion of the surgical therapeutic considerations as based upon our experimental investigations and clinical observations of twenty-six cases.

There are at present two available procedures in the surgical treatment of scleroderma: sympathectomy and parathyroidectomy. This in itself aptly, if trenchantly, suggests the confusion that exists in the etiology and pathogenesis of the condition. Both procedures, however, are based upon a rational consideration of certain facts and observations which seem to have pathogenic significance.

*On leave of absence, Department of Surgery, Tulane University Medical School, New Orleans, La.

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THEORETIC BASES FOR SURGICAL MEASURES APPLIED TO THE SYMPATHETIC APPARATUS

It has long been observed that there is a certain type of scleroderma which in its onset closely resembles a mild or atypical Raynaud's disease. As a matter of fact, in a large number of cases the diagnosis first made is Raynaud's disease, and subsequently the characteristic dermatologic features appear and the diagnosis is then changed to scleroderma. Kaufman[1] states that the symmetrical type of scleroderma, usually confined to the extremities, often begins with symptoms of Raynaud's disease; and O'Leary and Nomland[2] in a clinical study of 103 cases of scleroderma found that there was an antecedent vasomotor disturbance in over one-third. We have noted this same phenomenon in the majority of cases which we have observed.

Aside from the fact, however, that in a large number of cases of scleroderma there is a preceding history of vasomotor disturbances closely simulating Raynaud's disease, there are other facts which lend support to this conception of its pathogenesis. Although there has been a paucity of necropsy examinations in the study of scleroderma, nevertheless the histopathologic investigations that have been made show definitive changes in the arterioles and capillaries in certain forms of scleroderma. Matsui[3] reported detailed examinations of six patients and found definite changes not only in the small cutaneous arteries but also similar degenerative changes in the lungs, kidneys, and endocrine glands. As a result of these studies, he opined that scleroderma was probably a manifestation of endocrine dysfunction. Sannicandro[4] also noted these pathologic manifestations. Although Brown, O'Leary, and Adson[5] made similar observations in sections of skin studied, they state, however, that there was considerably more cellular infiltration both within and around the small cutaneous vessels in those patients with the vasomotor type of scleroderma. An endarteritis of the peripheral vessels was also reported by Rake[6] in the case which he studied in detail and which was of the vasomotor type.

The interesting observations made by Brown and O'Leary[7] and Brown, O'Leary, and Adson[5] are especially noteworthy in this respect. In their microscopic studies of the capillaries in the nailfold, they found a marked diminution in the number of open capillaries for each unit area of skin, with definite disturbances in the flow of blood through the loops. Slight lowering of environmental temperature produced slowing or even an arrest in the flow of blood, thus reflecting the exaggerated tonus of the arterioles. They came to the conclusion that the diminished vascularity of the skin in certain forms of scleroderma was due not only to the occlusive disease of the smaller vessels but also to the significant factor of sympathetic hypertonia of the arterioles. One of us[8] with Fontaine, in 1929, showed by oscillometric studies this characteristic vasospastic element in certain forms of scleroderma. The oscillometric

indices demonstrated very clearly the marked influence of environmental temperature, so typical of Raynaud's disease. The observations reported by Johnson and Hedges[9] are also of interest in this regard. They reported a case of Raynaud's disease complicated with scleroderma and sclerodactylia in which they made circulatory studies with a special finger plethysmograph. Their investigations demonstrated that the circulation was persistently less than normal in the fingers, even in the absence of an attack, and that peripheral vasodilation could be induced with local heat.

In recapitulation, the rationale for the conception that the sympathetic apparatus is of pathogenic significance in certain forms of scleroderma, and therefore sympathectomy is indicated as a therapeutic procedure, is based upon the following facts and observations: In a large number of cases of scleroderma the onset is characterized by vasomotor disturbances which so closely resemble Raynaud's disease that this diagnosis is frequently made. Clinical corroboration of this vasospastic element is demonstrated by the spontaneous improvement which often follows febrile reactions and the transportation of these patients to warmer climates. Histopathologic studies clearly reveal definitive vascular changes, and the pronounced influence of the environmental temperature upon the flow of blood in the skin is confirmatory evidence of the pathologic hypertonia of the arterioles.

CLINICAL CONSIDERATIONS OF SYMPATHECTOMY

Because clinical observations indicated that there was a vasospastic element in certain forms of scleroderma one of us,[10] in 1922, proposed the interruption of sympathetic fibers to the vessels as a therapeutic procedure in this form of the disease. The first practical realization of this method of treatment was made by Brüning.[11] Other reports followed by Enderlen,[12] Horn,[13] Kappis,[14] Stahl,[15] Kment,[16] Lehmann,[17] Muller,[18] and more recently by Adson, O'Leary, and Brown.[19] As is usually the case when a new procedure is quickly adopted before a more rational comprehension of the underlying physiologic principles is developed, the results have been varied and contradictory. Some reported brilliant results, while others observed complete fiascos. On December 5, 1924, one of us with Fontaine[20] performed our first sympathectomy upon a patient with scleroderma, which resulted in definite improvement. Since then we[8, 21, 22] have performed others, which are reported elsewhere in detail. We present here a brief summary, with follow-up reports, of all the cases we have performed up to the present time in this clinic.

CASE 1.—Woman, fifty-six years of age. For thirteen years she had had symptoms of sclerodactylia and gout. Skin of face and neck was atrophied; skin of hands was thick, indurated, tense, and painful, and there was stiffness of the joints of the fingers. Various forms of medical treatment had failed. Following bilateral

perihumeral sympathectomy on Dec. 5, 1924, there was complete relief of pain, the skin of the hands became more flexible, and mobility of the joints increased. In April, 1925, right cervical sympathectomy and ramisection were performed on the left side. Following this, the skin of the face and neck became hyperemic and more flexible and the condition of the hands continued to improve. When last examined, April, 1929, four years after last operation, the skin of the face, neck, and hands had maintained the same improvement, but the gout was not influenced.

CASE 2.—Woman, forty-six years old. During the past two years scleroderma of the face, neck, and hands had developed. Finger joints were almost immobile. On May 5, 1925, left cervical ramisection was performed. Two weeks later the same procedure was followed on the right side, together with bilateral perihumeral sympathectomy. Following this, the skin of the hands, which had previously been cold and cyanotic, became warm and had a more normal color. The skin of the face and neck became more flexible and the joints of the fingers were more mobile. When reexamined in 1934, nine years later, the patient appeared completely cured. Skin of face, neck, and hands was normal and joints had regained total mobility.

CASE 3.—Woman, fifty-four years old. For the past twenty years she had had vasomotor disturbances in the hands and feet, resembling Raynaud's disease. Two years previous to admission to the hospital, she noted areas of redness and induration of the skin of the left leg and later similar areas on the right leg and upper extremities. On examination, sclerodermatous changes were observed on both upper and lower extremities with slight involvement of the face. Right cervical sympathetic ramisection was done on June 5, 1925, and on June 24, left perifemoral sympathectomy. Following these operations there was hyperemia, and the skin of the right upper and left lower extremities became less tense and indurated, pain disappeared, and the joints of the fingers were more mobile. In 1929, four years after operation, the patient wrote that she still retained the same degree of improvement.

CASE 4.—Woman, twenty years old. Condition began two years previously, with redness and induration of the skin, and arthralgia. On examination, it was observed that she had pronounced generalized scleroderma with involvement of almost all the joints. Opening her mouth was extremely difficult, and there was almost complete immobilization of the joints of the hands, wrists, and elbows. On June 20, 1928, left cervical sympathectomy was performed and five days later the operation was repeated on the right side. Ten days later the patient was dismissed from the hospital; at that time the skin of the face had shown some improvement and the patient could open her mouth much more easily. Six months later the mother wrote that there was apparently no amelioration.

CASE 5.—A woman, forty-nine years of age, had marked generalized scleroderma, immobilization of nearly all joints, cataracts, and digestive disturbances. She had considerable pain in her hands, which were cyanotic and cold. Extirpation of the right cervical sympathetic chain on Dec. 7, 1928, gave no improvement.

CASE 6.—Woman, fifty-three years of age. Four years previous to admission, she began having vasomotor disturbances in her hands, resembling Raynaud's disease. Shortly afterward sclerodermatous changes developed which at the time of examination involved the face, neck, upper part of chest, hands, and forearms. There was some pigmentation on the dorsum of the hands, with partial immobilization of the finger joints. Blood calcium was 0.126 (Hirth). Radiographic studies revealed marked osteoporotic changes in the phalanges, carpal bones, and lower part of the radius and ulna. Following resection of the left inferior cervical ganglion on Feb. 24, 1933, there was definite improvement in the skin of the left hand and left side of the face, with increase in mobility of the fingers on the left hand. After resection of the right cervical sympathetic chain on Feb. 16, 1934, there was similar

improvement on the right side. Mouth could be opened much better. In December, 1935, examination revealed that the patient continued to show the same degree of improvement.

CASE 7.—A woman, fifty-two years old, had suffered for ten years with characteristic vasomotor disturbances of Raynaud's disease. Recently she began to develop sclerodermatous changes in her hands. On April 10, 1933, extirpation of the right inferior and middle cervical ganglions was performed. Examination in December, 1935, revealed no evidence of scleroderma in the extremities and the patient has had no more vasomotor disturbances, but sclerodermatous changes were definitely present on the thorax and abdomen. This case clearly demonstrates the futility of sympathectomy in the generalized forms.

CASE 8.—Woman, fifty-one years of age. Four years previously she noted slight induration and pigmentation of the skin of all extremities. Later vasomotor disturbances developed in her fingers. Examination showed marked generalized scleroderma of the face, neck, chest, and extremities, with pigmentation on the hands. Finger joints were almost completely immobilized. Wrists were also involved, with considerable pain. The lower extremities were less involved. Radiograms revealed osteoporotic changes in the phalanges and carpal bones. On April 6, 1933, resection of the right inferior and middle cervical ganglions was done, but there was no improvement immediately after the operation. Patient died suddenly on April 29, 1934, and autopsy revealed pneumonia and adhesive pericarditis.

CASE 9.—A woman, forty-three years of age, had complained for three years of vasomotor disturbances in the hands, feet, and nose. Sclerodermatous changes began two years later, especially marked in the hands, forearms, and face, with less involvement in the lower extremities, and pigmentation. There was stiffness of the wrist and finger joints, and considerable pain. Right cervical sympathectomy on June 14, 1933, caused very little improvement afterward. Examination on Feb. 17, 1935, showed no improvement.

CASE 10.—A woman, forty years of age, had complained for the past nine years of vasomotor disturbance in her fingers and toes, resembling Raynaud's disease. Shortly after this began she noted sclerodermatous changes with pigmentation, which at present is almost generalized. There was involvement of the joints of the upper extremities, with considerable pain. Calcemia 0.100 (Hirth). After resection of the right inferior cervical sympathetic ganglion on Sept. 8, 1933, there was moderate improvement in the condition of the right upper extremity and both lower extremities. In May, 1934, this same degree of amelioration was still present.

CASE 11.—Woman, twenty-eight years of age. For four years she has had vasomotor disturbances typical of Raynaud's disease. For the past two years sclerodermatous changes have developed, which at the time of examination were most marked in the face, neck, forearms, and hands, with pigmentation and limitation of motion in the joints of the fingers, wrist, and elbow. Blood calcium 0.109 (Hirth). On July 22, 1933, resection of the right inferior cervical sympathetic ganglion was done. Five days later, there was definite improvement in the condition of the skin and mobility of the joints on that side. On Aug. 4, 1933, a similar operation was performed on the left side. An examination, Nov. 9, 1934, showed marked improvement. Pigmentation had disappeared. The skin of the face, neck, and upper extremities was more flexible, warm, and pink. Movement of joints was considerably improved, and vasomotor disturbances had disappeared.

CASE 12.—Woman forty-two years of age. Four years before admission she began to complain of vasomotor disturbances which were not typical of true Raynaud's disease. Shortly afterward sclerodermatous changes developed. On examination, scleroderma with pigmentation was found most marked in the lower extremities

up to the thighs and in the upper extremities, but more pronounced on the right side. Limitation of motion of the shoulder and elbow joints. On Dec. 2, 1933, left lumbar sympathectomy was performed. Following the operation improvement was such as to justify similar procedure on the right side, which was performed on Jan. 26, 1934. Similar improvement in the skin condition was noted. On Feb. 12, 1934, a resection of the right inferior cervical sympathetic ganglion was followed by definite amelioration in the right upper extremity and right side of the face. On March 2, 1934, a similar operation was performed on the left side. On Sept. 8, 1934, the patient was reexamined and marked improvement was still present.

CASE 13.—A woman, thirty-nine years old, had complained for two years of vasomotor disturbances in her fingers and toes, resembling atypical Raynaud's disease. For the past several months she had also noted sclerodermatous changes involving her face, neck, and hands. Following right inferior cervical sympathetic ganglionectomy on July 11, 1934, and a similar procedure on the left side ten days later, there was definite improvement on both sides. By Nov. 10 the condition was much improved. She was able to return to work as a piano teacher. When it became cold, however, she had slight vasomotor disturbances.

COMMENT

Of the 13 cases in which sympathectomy has been performed there was marked improvement in 5, 38.4 per cent, moderate improvement in 4, 30.7 per cent, slight improvement in 1, 7.6 per cent, and no improvement in 3, 23 per cent. It may be said in general that approximately two-thirds of the cases show some degree of improvement, and this reflects the general consensus. Mayo and Adson[23] arbitrarily divided their cases of scleroderma into three groups, depending upon whether the vasomotor phenomena preceded the disease, appeared simultaneously, or developed later. The greatest percentage of improvements following sympathectomy was obtained in the first group. They stress the importance of selecting those cases of scleroderma which show pronounced vasospastic phenomena, especially preceding the cutaneous manifestations. This is undeniably an important factor, and the best results will be obtained in that group of cases which might be termed the Raynaud-scleroderma syndrome. Even in this form of the disease, however, complete failures are not infrequent. One of our cases was characteristic of this type of scleroderma and after sympathectomy showed no improvement. Even in the others in which there was no improvement, vasomotor disturbances were definitely present. In the generalized, advanced cases sympathectomy is of little or no avail. Those cases most suitable for sympathectomy are the early ones in which the cutaneous lesions are not pronounced, in which the joints are not severely involved, and in which vasospastic phenomena are a conspicuous feature.

THEORETIC AND EXPERIMENTAL BASES FOR PARATHYROIDECTOMY

That a disturbance in the equilibrium of the sympathetic apparatus is not the only factor of pathogenic significance in scleroderma appears to be an ineluctable fact. It is obvious that there is a vasospastic ele-

ment, but the true etiology and pathogenesis remain yet unknown, and search must be made in another direction to determine what other factors play prominent rôles.

In 1929, Pautrier and Zorn[24] made a signal observation. They found a hypercalcemia in all of the 6 cases which they studied. Almost simultaneously Naegeli[25] made similar observations in 20 cases which he had studied. Michon and Bohême[26] noted an increase in blood calcium in 48 of 65 cases. One of us with Chinassi Hakki[27, 28] found hypercalcemia in 7 of 10 cases, and up to the present time in 20 cases of scleroderma which we have examined, the blood calcium was found to be: between 0.100 and 0.115 in 13 cases; between 0.89 and 0.099 in 4 cases; and between 0.087 and 0.088 in three cases.* Since then hypercalcemia in scleroderma has been reported by Milian et al.,[29] Weissenbach et al.,[30] Kennedy,[31] Pernet,[32] and others. On the other hand, hypercalcemia is not a constant finding and cases have been observed in which the blood calcium was normal or even below normal. In this latter group belong the cases cited by Durham,[33] Michon and Bohême,[26] and Lereboullet and Lelong.[34] Because these investigators have observed a normal or even subnormal blood calcium in patients with scleroderma, they have attempted to show that the hypercalcemia found in scleroderma is of little or no significance. We insist on the fact, however, that this does not depreciate the significance of hypercalcemia in scleroderma. Experimental investigations have shown that in chronic hyperparathyroidism the hypercalcemia is only temporary. Jaffe and Bodansky[35] have shown that in hyperparathyroid dogs the blood calcium is at first increased, but after a certain period of time, occasionally within three or four months, the blood calcium drops to normal and remains there in spite of the fact that the dogs are still in a state of hyperparathyroidism. We have observed this same phenomenon. In chronic hyperparathyroidism the hypercalcemia does not necessarily persist, and one is not justified in concluding that a parathyroid dysfunction does not exist in scleroderma simply because normal or subnormal blood calcium findings have been observed. Scleroderma should be considered not as an acute but rather as a chronic disturbance in parathyroid function, evolving over a long period of time, and when the patient is finally observed, the manifestation of hypercalcemia may no longer be present. Studies of the urinary calcium have revealed no significant changes which do not correspond with the blood findings.

The investigations which have been made upon the cutaneous changes occurring in experimental hyperparathyroidism are of considerable importance, and strengthen the theory that the parathyroids play a prominent rôle in scleroderma. In 1932, Selye[36] reported that the injection

*These determinations and all others given here were made by the procedure of Hirth, for which the normal figures are 0.089 and 0.099.

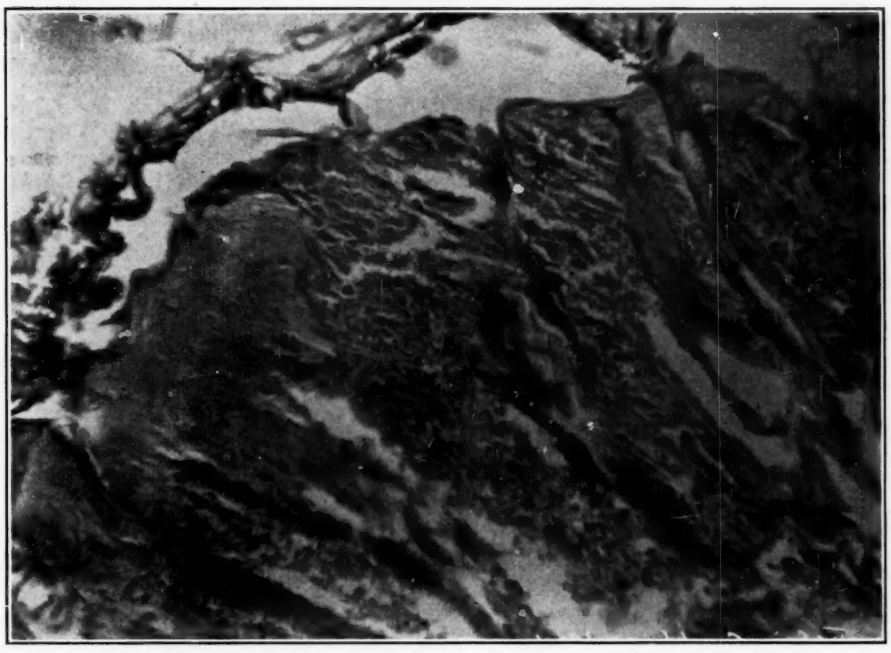

Fig. 1.—Photomicrograph of section of skin of a rat (two weeks old) which received 4 units of parathormone daily for four days. Haemalum-erythrosin-saffron stain. Note thinning of epidermis and degeneration of corium. (Collagen fibers indistinct. Pyknotic nuclei and sebaceous glands partially destroyed.)

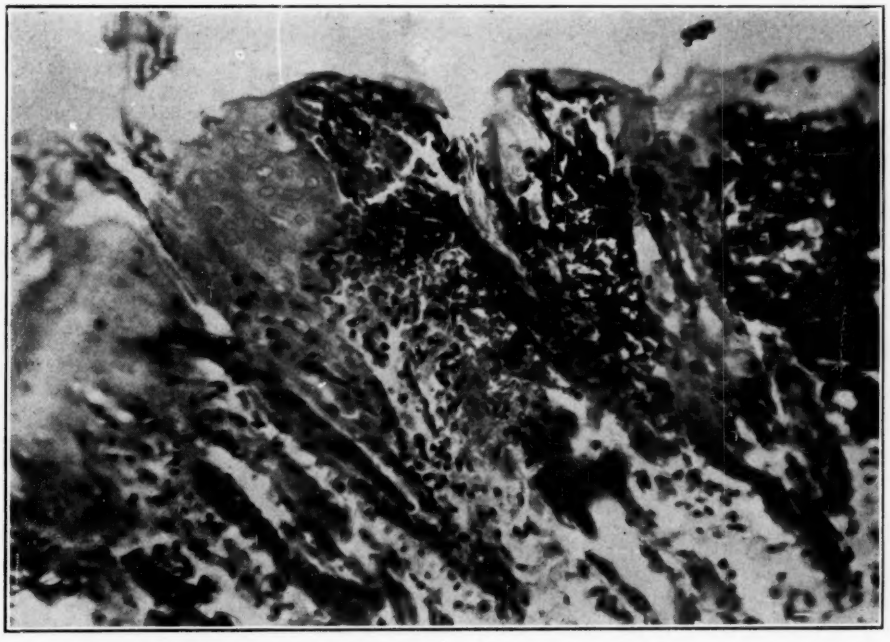

Fig. 2.—Photomicrograph of section of skin of same rat as shown in Fig. 1. Silver nitrate stain (de Kossa), showing marked calcium deposition in corium.

of parathormone in young rats, from one to two weeks old, produced cutaneous changes which anatomically resembled scleroderma, and in 1933 Shelling, Asher, and Jackson[37] confirmed these findings. With Sureyya[38] we made somewhat similar experimental studies and found that the injection of parathormone (Collip) in young rats (one to two weeks old) produced: (1) a marked arrest in growth; (2) thickening and induration of the skin with pronounced loss of hair; (3) an increase in the water content of the skin; (4) an increase of the calcium content of the skin of from two to three times the normal; (5) on histologic examination changes in the skin characterized by destruction and scar tissue, infiltration of the dermis with marked calcium deposition, and a pronounced atrophy and exfoliation of the epidermis. (Figs. 1 and 2.) These changes, however, seem to be transitory, because if the examinations are made later than several days after the injections, none of these manifestations can be demonstrated. Nevertheless, these findings indicate that cutaneous changes, which clinically and histologically resemble the scleroderma occurring in human beings, can be experimentally produced in young rats by the injection of parathyroid extract, and therefore strongly suggest a relationship between scleroderma and parathyroid dysfunction.

In that particular form of scleroderma in which the Thibierge-Weissenbach syndrome is found, calcium concretions frequently occur in the skin. We[39] have compared sections of skin taken from normal areas and from involved areas on the same patient in the localized form of scleroderma. These studies showed a 20 to 30 per cent increase in calcium content in the sclerodermatous regions. Roentgenographic studies of the skin of these patients also show such differences in density as could be accounted for by calcium deposition.

In the classical examples of hyperparathyroidism the skeletal changes are considered the most characteristic manifestations. It is only logical that if scleroderma is to be viewed as a manifestation of hyperparathyroidism, these characteristic skeletal changes should be found in this condition as well. In one of our previous publications[39] we called attention to the fact that in many cases of scleroderma there is a diffuse decalcification, as revealed by roentgenographic studies, which is not only limited to the spongeous portions of the bones but also involves the cortex. It is usually more pronounced in the extremities and is frequently localized in the hands and feet, especially the phalanges. Occasionally, we have observed cases in which the decalcification and rarefaction was so intense that the osseous structures of one or more phalanges could not be distinguished on the roentgenogram (Figs. 3 and 4). It must not be inferred from this that pronounced skeletal changes are always found in scleroderma, for we have observed many cases in which the roentgenographic studies revealed no osseous manifestations.

In some forms of scleroderma, however, characteristic skeletal changes are observed, clearly suggesting a disturbance in calcium metabolism and adding more prominence to the rôle played by the parathyroids.

In recapitulation, the rationale for the conception that the parathyroids (or rather hyperfunction of the parathyroids) are of pathogenic significance in scleroderma, and therefore parathyroidectomy is in-

Fig. 3.—Roentgenogram of hand of patient with generalized scleroderma. Note osteoporosis which is so pronounced in the terminal phalanges that they appear to have disappeared. Clinically the fingers were intact, and there was never any infection in them.

dicated as a therapeutic procedure, is based upon the following facts and observations: Hypercalcemia is frequently found in certain forms of scleroderma. Cutaneous changes clinically and histologically resembling scleroderma have been experimentally produced by injections of parathyroid extract. Studies of the skin in certain forms of scleroderma show an abnormal increase of calcium content. Skeletal changes

are not infrequently encountered in scleroderma, demonstrating a disturbance in calcium metabolism and reflecting parathyroid dysfunction. In addition to this, the pronounced hypotonia and asthenia, frequently observed in patients with scleroderma, are also suggestive of calcium metabolic disturbances and hyperparathyroidism.

Fig. 4.—Roentgenogram of the humerus, radius, and ulna at the elbow joint of a patient with generalized scleroderma. The partial osteoporosis is quite evident.

CLINICAL CONSIDERATIONS OF PARATHYROIDECTOMY

Because these clinical and experimental observations seemed to indicate that in scleroderma there is a definite physiologic disturbance in the calcium metabolism, suggesting a hyperfunction of the para-

thyroids, it seemed to us that parathyroidectomy was not only justifiable but a logical therapeutic procedure. It was with this basic consideration that we[40] performed our first operation of parathyroidectomy in January, 1931. As will be seen from a résumé of this observation (Case 21) given below, in spite of the fact that this patient had an advanced and generalized form of scleroderma, the operation was followed by a remarkable improvement. This encouraging result further justified the performance of parathyroidectomy. Several of these cases have been reported in detail elsewhere.[41] However, we are presenting a succinct account with follow-up reports of all the cases of scleroderma in which this procedure has been performed in this clinic.

It will be observed that the majority of these patients had a severe, generalized, and advanced form of scleroderma. Nevertheless of the 13 cases 5, 38.4 per cent, showed marked improvement, 7, 53.8 per cent, showed moderate improvement, and 1, 7.6 per cent, showed no improvement. Thus, of the total series definite improvement, to a greater or lesser degree, followed operation in over 90 per cent.

The one case showing no improvement deserves some comment (Case 15). This patient had Addison's disease in addition to an advanced scleroderma, and immediately following the operation there was an undeniable amelioration in the dermatologic manifestations. However, the patient lived only two months following the intervention. She probably succumbed to the Addison syndrome, and strictly speaking should not be considered as unimproved following parathyroidectomy. Thus, it can be said that actual improvement followed the operation in all of the cases.

It is a well-established fact that one of the most important criteria in the evaluation of a particular procedure is the length of time improvement is maintained following its application. In this series it will be noted that 6 patients have been observed from approximately two to five years after surgical intervention. All of these patients have not only maintained the improvement which immediately followed the operation, but have continued to improve. One of these (Case 14) was just recently examined, five years after operation, and it can be said that she has been completely relieved of all previous manifestations of the disease. One other patient (Case 17), when last observed two years following operation, also revealed no evidence of the previous sclerodermatous condition.

As will be observed from the cases listed, in several of the patients sympathectomy has been combined with parathyroidectomy. In previous publications one of us[42, 43, 44] has discussed the indications for the combination of these two procedures in scleroderma. It may be stated that, in general, sympathectomy should be combined with para-

thyroidectomy in those patients characterized by symmetrical lesions, especially of the extremities, and having typical vasomotor disturbances.

The technical considerations of parathyroidectomy have been discussed in detail by one of us[45] in a previous publication. Those who have had even the slightest experience with surgery of the parathyroids appreciate fully the technical difficulties that are encountered. Not infrequently it is impossible, even with meticulous dissection, to find these small glands. Under such circumstances we have found that a substitute procedure is the ligation and section of the inferior parathyroid arteries. It seems that this procedure, by diminishing the blood supply to the glands, suffices.

CASE 14.—Woman, aged sixty years. She began complaining, at the age of thirty-seven, of pain and a burning sensation in the skin over the right external malleolus. Skin in this region was dry, indurated, and had a cyanotic hue. For the past eighteen months similar disturbances developed in the left leg, and pain finally became so intense that she was forced to stop working. On examination advanced sclerodermatous changes were found on the legs, especially involving the dorsum of the feet, ankles, and the lower half of the legs. Her ankles were almost completely immobilized. Blood calcium 0.112. On March 27, 1931, we ligated and sectioned the right inferior thyroid artery. On the day following operation the patient seemed to be improved. Skin developed a more normal color. Blood calcium on April 1, 1931, was 0.087. When the patient was dismissed from the hospital ten days after operation, she seemed considerably improved. She had no more pain and could move her ankles with ease. When reexamined March 18, 1936, about five years after operation, she had no more pain, her skin was almost normal in color and flexibility, and there was no limitation in motion of the ankles. She appeared completely cured.

CASE 15.—Woman, aged thirty-four years. For three years she had complained of vasomotor disturbances in her hands. There were marked sclerodermatous changes of the face, neck, forearms, hands, and fingers. The rest of her body was also involved to a lesser degree, and the skin over the entire body had a bronzed discoloration similar to that in Addison's disease. She felt extremely fatigued and complained of constant pain in her knee and shoulder joints. Blood calcium 0.113. She had been treated for the past three weeks with adrenal extract in an attempt to relieve Addison's syndrome, and this phase of her condition seemed ameliorated, but the scleroderma appeared to be aggravated. On June 3, 1931, the right inferior parathyroid was found and removed. (Confirmed by histologic examination.) A few days following the operation she appeared considerably better. She was able to move her fingers more easily and no longer complained of pain. Blood calcium on July 3, 1931, was 0.089 and on July 10, 0.090. Two months later the patient returned to the hospital and was found to be much worse; she was in such a gravely ill state as not to justify any intervention. She rapidly became worse and died in three weeks. Autopsy not obtained.

CASE 16.—A woman, thirty-two years old, complained of vasomotor disturbances resembling Raynaud's disease in her hands and feet since childhood. For three years she has developed sclerodermatous changes which, on examination, involved particularly her hands and the lower half of her legs. Finger joints were partially immobilized. Blood calcium 0.112. On May 26, 1932, her right inferior parathyroid was and removed. (Confirmed by histologic examination.) On the day after operation discoloration of the skin disappeared, and when the patient was dismissed from the

hospital she seemed considerably improved. She had no more joint pains; her temperature, which had previously been slightly elevated, was normal; her skin was much more flexible, and the finger joints could be moved with ease. Blood calcium dropped to 0.089. She was seen again in December, 1935, about two and one-half years after operation, and marked improvement was still present.

CASE 17.—A girl, eighteen years old. At the age of thirteen she began to complain of vasomotor disturbances in her fingers which resembled typical Raynaud's disease. At sixteen she developed sclerodermatous changes, involving her face, neck, and shoulders. Her skin was thick, indurated, edematous, and tense. Blood calcium was 0.102. On June 7, 1932, the right inferior thyroid artery was sectioned between ligatures. Parathyroids were not found. She seemed much improved immediately following operation. Her skin returned to normal, and the blood calcium was 0.089. Patient, when seen again about two years after operation, appeared completely cured.

CASE 18.—A woman, fifty-four years of age, had had vasomotor disturbances typical of Raynaud's disease for ten years. Simultaneously she developed sclerodermatous changes which on examination appeared pronounced and generalized. Her face was masklike and devoid of expression. Her mouth could be opened only slightly and speaking was very difficult. Hands were typically deformed and pigmentation was generalized. She also had digestive disturbances and involvement of the joints. Blood calcium was 0.104. On Sept. 10, 1934, operation was performed. Parathyroids were not found but both inferior thyroid arteries were sectioned between ligatures. She showed improvement on the day after operation. Her hands and feet were warmer and three weeks later she seemed considerably improved. Her mouth could be opened more easily and the skin of her face was more flexible. On March 21, 1935, resection on both sides of middle cervical sympathetic ganglions was done. When last examined in January, 1936, there was very little improvement over that previously stated.

CASE 19.—Woman, aged fifty-three years, had complained of vasomotor disturbances in her hands and feet, resembling atypical Raynaud's disease, for seven years. Almost simultaneously she noticed beginning sclerodermatous changes, which on admission were found to be generalized, with marked pigmentation on the upper extremities. Fingers were immobilized in semiflexion. Wrists, shoulder joints, and knees were almost completely immobilized. Opening the mouth was very difficult. Blood calcium was 0.124. An x-ray film showed marked osteoporotic changes in the hands. On Feb. 24, 1933, bilateral lumbar sympathectomy was performed and on March 11, 1933, right inferior parathyroidectomy (histologically verified). She was last observed in December, 1935. Her condition was much improved. Whereas previous to operation she was forced to remain in bed, she is now able to walk and get about without difficulty. Pain in the extremities has disappeared and also the pigmentation (except in the lower extremities). Her mouth could be opened with greater east, and the skin of her face was more flexible. Also immobility of the fingers was less marked.

CASE 20.—Woman, forty-one years of age. For twelve years she had complained of vasomotor disturbances in her hands, characteristic of Raynaud's disease. About the same time she began to develop sclerodermatous changes. On examination, scleroderma was found to be markedly advanced, involving almost the entire body, with pigmentation and joint involvement. She was in constant pain and in poor general condition. Blood calcium was 0.076. X-ray examination revealed generalized osteoporotic changes, especially marked in the bones of the hands. On Aug. 30, 1933, a left lumbar sympathectomy was performed. Following this, the patient complained of less pain in her left leg. Right lumbar sympathectomy on Sept. 26, 1933, was followed by amelioration of the pain in the right leg. Movement of joints of the

legs was definitely improved. Right inferior cervical ganglionectomy on Feb. 26, 1934, was followed by similar improvement in the right upper extremity. April 24, 1934, a similar operation was performed on the left side. Oct. 1, 1934, two inferior parathyroids were removed (confirmed histologically). Three weeks later patient showed marked improvement in general. Pigmentation disappeared and she no longer complained of joint pains. She was able to move her joints to greater amplitude and more easily. The skin was much more flexible and her mouth could be opened easily. Although bedridden previous to operation, she is now able to get about easily and has gained weight.

CASE 21.—Woman, fifty-seven years of age. For the past twelve years she has complained of vasomotor disturbances resembling typical Raynaud's disease. About the same time she developed sclerodermatous changes which at the time of admission were very advanced and especially marked over the face, neck, hands, and feet. Fingers were completely immobilized in semiflexion. Blood calcium was 0.110. Jan. 15, 1931, left cervical sympathectomy was performed together with section between ligatures of the left inferior thyroid artery. There was considerable amelioration in the left upper extremity following this operation. On Jan. 23, 1931, resection of the right inferior cervical ganglion and removal of the right inferior parathyroid (histologically confirmed) were performed. Blood calcium on Jan. 26, 1931, was 0.082. Following operation, the patient showed similar improvement on the right side. Her skin began to have a more normal appearance and that on the face and neck became more flexible; she was also able to move her fingers with greater ease. She had no more pain except to a slight extent in her feet and legs. On Feb. 10, 1931, we performed a bilateral periarterial sympathectomy of the external iliacs. On dismissal from the hospital she had no more pain. When last heard from in April, 1931, the patient was still considerably improved.

CASE 22.—Woman, thirty-four years old. At nineteen years of age she began having vasomotor disturbances typical of Raynaud's disease. No long afterward she developed sclerodermatous changes involving the face, neck, and hands. Blood calcium was 0.115. On Sept. 17, 1931, resection of the right inferior cervical sympathetic ganglion was performed, followed on Sept. 26 by left cervical sympathectomy and removal of the left inferior parathyroid gland (histologically confirmed). Following operation the patient showed marked improvement. Blood calcium dropped to 0.090. When examined again in June, 1932, the skin on the face and neck had returned to normal, and that on the hands was much improved but there was still some cyanosis in the hands. On June 22, 1932, bilateral perihumeral sympathectomy was performed and following this, the hands became warm and pink. Last observed July 18, 1935, almost four years after operation. Skin of face and neck appeared normal. Mouth could be opened normally. Previous improvement was maintained.

CASE 23.—A woman, twenty-seven years of age, began to notice sclerodermatous changes one year previously, with some vasomotor disturbances in the hands. Scleroderma was especially marked on the face, neck, hands, and forearms. Her mouth could be opened only with difficulty, and movement of fingers was very limited. There was slight involvement over the ankles. Blood calcium was 0.110. On Nov. 14, 1931, the left inferior parathyroid was removed (histologically confirmed). Patient seemed much improved, skin appeared more flexible, and pain in the legs had disappeared. Blood calcium dropped to 0.094. On Nov. 26, 1931, resection of the right inferior cervical sympathetic ganglion was performed. Patient was seen again Jan. 23, 1932, and showed marked improvement. She had no more pain, her skin was more flexible with more normal hue, and her fingers had regained complete mobility.

CASE 24.—Man, forty-two years old. Sclerodermatous changes developed in past year and a half. At the time of admission scleroderma was very pronounced and

generalized. The patient's face was like a mask. His fingers were stiff and like stone. He complained of marked pain in all joints. He had digestive disturbances and diarrhea. On Feb. 13, 1934, blood calcium was 0.095, and on May 20, 1934, it was 0.091. Over a three-day period he ingested 2.72 grams of calcium and excreted 3.55 grams. On Dec. 15, 1934, the urinary calcium was found to be 0.225 gram per liter and 0.222 gram during twenty-four hours. On May 28, 1935, the inferior parathyroids were removed (histologically confirmed). Blood calcium on June 4, 1935, was 0.084. Following operation, the skin condition showed considerable improvement. When seen again in January, 1936, the improvement in the skin was even better, but he still complained of joint pains.

CASE 25.—A man, fifty-five years of age. Sclerodermatous changes began about one year previously. On admission he had advanced scleroderma, involving almost the entire body, being especially marked on the face, back, and upper extremities. His hands were completely immobilized, with fingers in semiflexion. On Oct. 20, 1935, the blood calcium was 0.086; the urinary calcium was 0.162 per liter, and 0.287 per twenty-four hours. Calcium determinations of the skin revealed 0.139 gram per 1,000 grams (fresh), and 0.503 (ashes). On Nov. 29, 1935, both inferior parathyroids were removed (histologically confirmed). There was marked improvement following operation. To increase the improvement in the upper extremities resection of the inferior cervical sympathetic ganglions was performed on the left and right sides, Dec. 12 and 28, 1935, respectively. On dismissal from the hospital Jan. 9, 1936, the patient showed definite improvement in general. The skin was much more flexible and finger joints showed greater amplitude of motion. Blood calcium on Dec. 5, 1935, was 0.082. Calcium determinations of the skin were 0.199 gram (fresh) and 0.465 gram (ashes); water content 57.2 per cent. Similar determinations of the muscles gave 0.123 gram (fresh) and 0.491 gram (ashes).

CASE 26.—A woman, forty-three years old, had, for three years, complained of vasomotor disturbances in the fingers, similar to Raynaud's disease. Shortly after this she began to develop sclerodermatous changes, which upon admission were found to be generalized, being especially pronounced on the face, neck, and hands. With onset of scleroderma she began losing teeth which had previously been in good condition. She also complained of digestive disturbances and alternating constipation and diarrhea. X-ray examination revealed marked decalcification in the bones of the hands. Blood calcium was 0.086; urinary calcium was 0.088 gram per liter and 0.058 gram per twenty-four hours. Calcium determinations of the skin showed: 0.145 gram (fresh) and 0.412 gram (ashes). Water content 64.7 per cent. On Feb. 10, 1936, two inferior parathyroids were removed (histologically confirmed) and right cervical sympathectomy was performed, and on Feb. 27, 1936, she had a left cervical sympathectomy. Following operation, there was moderate improvement in the condition of the skin, especially in the face, neck, and thorax, but no improvement in the condition of the joints. Blood calcium 0.084. Patient was last examined April 3, 1936, at which time the finger joints were more mobile and the skin condition in general was much improved.

SUMMARY

1. The etiology and pathogenesis of scleroderma remain yet unknown and up to the present time nonsurgical treatment has been of little or no avail.

2. The rationale for the conception that the sympathetic apparatus is of pathogenic significance in certain forms of scleroderma and, therefore, sympathectomy is indicated as a therapeutic procedure, is discussed in detail. In this so-called Raynaud-scleroderma type of

syndrome histopathologic studies reveal definite vascular changes and clinical investigations show evidence of pathologic hypertonus of the arterioles.

3. Résumés of 13 cases of scleroderma in which we have performed sympathectomy are presented. Improvement to a greater or less degree followed operation in approximately two-thirds of the cases. One is forced to the conclusion that a disturbance in the equilibrium of the sympathetic apparatus is not the only or even the most significant factor in the pathogenesis of scleroderma.

4. The rationale for the conception that a chronic hyperfunction of the parathyroids is of pathogenic significance and, therefore, parathyroidectomy is indicated as a therapeutic procedure, is discussed in detail. Clinical and experimental investigations clearly demonstrate a definite disturbance in calcium metabolism, thus reflecting exaggerated physiologic function of the parathyroids.

5. Résumés of 13 cases of scleroderma in which we have performed parathyroidectomy are presented. On several of these patients sympathectomy was also performed. Improvement to a greater or less degree followed operation in over 90 per cent of the cases. Two of the patients, examined two and five years respectively after operation, could be considered as cured. All of the patients had rather severe and generalized forms of scleroderma. Only one patient was considered to have shown no improvement, although amelioration was observed immediately after operation, but the patient died two months later of the complicating Addison's disease.

6. In our experience parathyroidectomy is the procedure of choice in the treatment of scleroderma. It is unjustifiable to state definitely that scleroderma is caused by hyperparathyroidism. But clinical and experimental evidence supports the view that a chronic hyperparathyroidism does exist in scleroderma, and parathyroidectomy seems to ameliorate the condition. Sympathectomy may be combined with parathyroidectomy in those patients characterized by symmetrical lesions, especially of the extremities, and in those having typical vasomotor disturbances.

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THE SPHINCTER OF ODDI IN MAN AND CERTAIN REPRESENTATIVE MAMMALS*

EDWARD A. BOYDEN, PH.D. (MED.SC.), MINNEAPOLIS, MINN.
(From the Institute of Anatomy, University of Minnesota†)

NOTWITHSTANDING the mixed aura of credulity and suspicion that surrounds what one surgical text has called "the rather mythical sphincter of Oddi," the experimental work of the last twenty-five years points unmistakably to the existence of an intrinsic musculature which under certain morbid conditions can produce biliary stasis. Although, at first, attention was focused upon the reaction of this muscle to cholecystectomy,[1-5] in recent years greater emphasis has been placed upon its dysfunction in the presence of an intact gallbladder—upon a dyskinesia of the biliary tract that may induce gallbladder distress or colic even in the absence of calculi or of inflammation.[6-10]

In view of these extensive studies, why is it that skepticism still exists regarding the sphincter of Oddi? The answer is twofold. In the first place it has been exceedingly difficult to separate its action from that of the duodenal muscle which surrounds it—a feat that has been rarely accomplished, experimentally. Second, on account of the small size, position, and complexity of the sphincter, it has been equally hard to demonstrate its independence, histologically. Even Nuboer,[4] who has provided the only graded series of sections through the adult human sphincter, has confused intestinal tunics with the musculus proprius of the bile duct. Nor has such an imaginative diagram as that found in Cunningham's *Anatomy* (Fig. 915, 1928) made it any easier to comprehend. The matter has been still further complicated by the most amazing species differences—that factor which so long retarded our understanding of the functions of the gallbladder.

Believing, therefore, that some simpler anatomic approach to the problem was needed, the writer, some time ago, started a series of comparative studies on the embryologic development of the choledochal musculature, of which this paper represents a preliminary account.

DEFINITION OF THE SPHINCTER OF ODDI

According to Francis Glisson (1654), who first observed this "locking" mechanism, the sphincter consists of "ringlike fibers which occupy not only the opening [of the bile duct] itself but also the whole

*Presented at the Durham meeting of the American Association of Anatomists, April, 1936. The references to the human sphincter are based upon the studies of Schwegler and Boyden.[18]

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oblique tract [through the intestinal wall]."* So also to Oddi[12] it is "a more or less pronounced bed of circular fibers encircling the choledochal canal—which one is able to consider as almost completely independent, if one excepts some slender loops which lose themselves between the fibers proper of the intestine." Incidentally, Oddi's name has been applied to it not because he was the first to examine it microscopically—that distinction belongs to the American anatomist Simon H. Gage[13]—but because he demonstrated it in a variety of animals and because he was the first to measure its resistance, to show that removal of the gallbladder caused marked dilatation of the bile ducts, and to postulate that dysfunction of this occluding apparatus might explain certain morbid affections of the biliary tract. With the more complete information now at our disposal it has come to be realized that the longitudinal fibers of the sphincter may be as important as the circular fibers—at least, in some species—hence the concept that the sphincter of Oddi is an ejaculating as well as an occluding mechanism.[6, 14] It is necessary, therefore, to define it as the entire musculus proprius of the terminal portion of the bile channel and of the associated pancreatic duct (of Wirsung), if the latter is present.

THE RETROGRESSION OF THE AMPULLA

Fig. 1 presents a group of diagrams showing how certain mammals may be arranged in a series to illustrate the progressive involution of the ampulla of Vater.

In the opossum, according to DuBois and Hunt,[15] the terminal apparatus consists of a duct of the ampulla *(D. amp.)*, coursing obliquely through the intestinal wall, of an ampulla itself *(Amp.)*, which lies wholly outside the intestine, and of such distal portions of the two ducts as are enclosed in a common musculature.

In the guinea pig,[16, 17] most of the ampulla has been taken into the intestinal wall, but it lies superficially, bulging out at the level of the intestinal muscle (Figs. 1-4). Its duct empties at right angles to the ampulla (Fig. 2). The duct of Wirsung, which by analogy with other rodents should join the bile duct outside the intestinal wall, never appears at any stage. Westphal[6] compared the ampulla to the pyloric antrum of the stomach because it undergoes peristalsis. His other name for it (portio duodenalis), however, is misleading, for the papillary portion is also duodenal.

In man,[18, 19] the confluence of bile and pancreatic ducts starts outside the intestine, but in the course of development the zone of junction becomes drawn into the wall so that in most adults the ampulla is a vestigial structure. According to Mann and Giordano,[20] 76 per cent

*For an account of this region as viewed by the older anatomists (Vesalius, Fallopius, Glisson, Bianchi, Vater, Haller, Santorini, etc.), see Boyden.[11]

of individuals have an ampulla 2 mm. or less in length—a fact which has led these authors to conclude that regurgitation of bile into the pancreatic duct must be of rare occurrence.

In the dog,[21] there is no ampulla, since even in the embryo the ducts open separately into the duodenum.

These illustrations suffice, perhaps, to show what varied conditions exist in one class of vertebrates and how different the sphincter must be in the four species. For convenience, the muscle will now be described, regionally.

THE MUSCULUS PROPRIUS AMPULLAE

In the opossum, the ampulla of Vater and its duct are clothed with a thick, double layer of smooth muscle (consisting of an outer circular and an inner longitudinal coat), which starts well above the junction

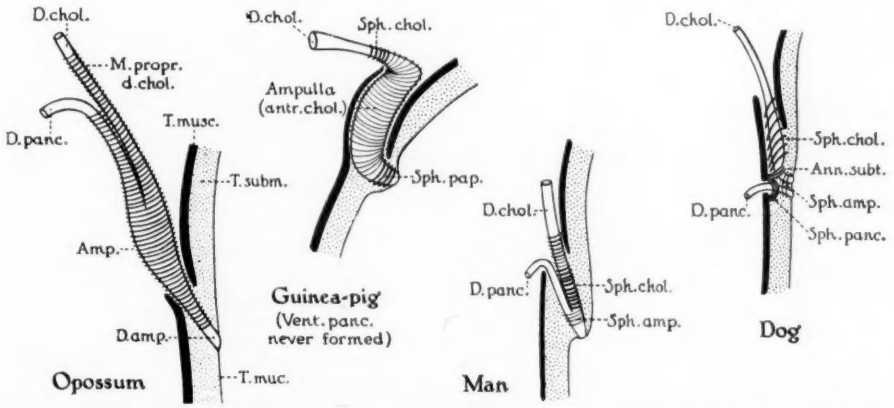

Fig. 1.—Posterior views of the pars intestinalis of the common bile duct in four mammalian species, based upon unpublished reconstructions of fetal stages. Heavy black lines: tunica muscularis of duodenum; transverse lines: circular fibers of musculus proprius of ducts and ampulla. (Orientation same as in Fig. 149b, Braus' Anat. d. Menschen, Vol. II, 1924.)

of the lumina of bile and pancreatic ducts and continues through the intestinal wall to a zone near the orifice of the ampullary duct. Its most striking and significant feature, as brought out by DuBois and Hunt,[15] is the complete separation of its musculature from that of the duodenal wall throughout its intramural course. Wherever the two muscle layers approach each other a connective tissue layer intervenes. Even in the new embryonic preparations of these authors (which I have had the privilege of examining in advance of publication) the margins of the aperture in the intestinal muscle through which the ampulla passes, make little if any contribution to the sphincter of Oddi; i.e., embryonic and adult patterns are essentially alike. One cannot overestimate the importance of these observations. They show that in a primitive mammal the biliary musculature is independent of that of the intestine. Physiologically, the ampulla and its duct seem

to be primarily a mechanism for ejaculating bile through the intestinal wall (see authors' description of peristaltic waves[15, 22]) since the gallbladder has a weak musculature and an extremely narrow outlet into the cystic duct.*

In the guinea pig the intrinsic muscle of the ampulla (or antrum) is so blended with the circular muscle of the intestine that in the adult the two layers cannot be differentiated except at the edges or at the two ends of the ampulla. The probable explanation for this is that in the embryo the antrum remains at the level of the intestinal musculature, lying athwart the window in the tunica muscularis, so that

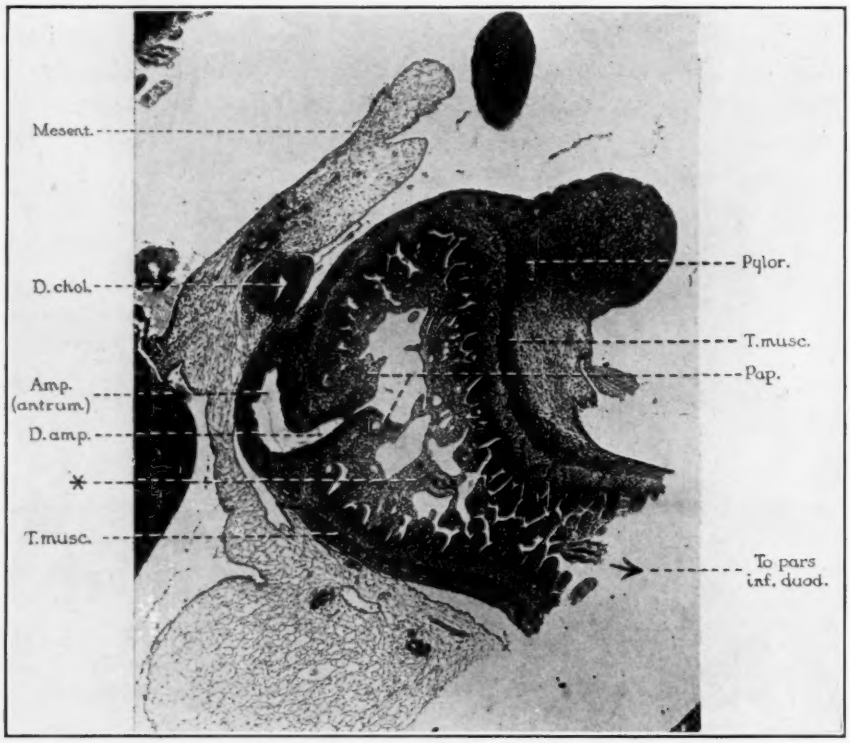

Fig. 2.—Low power photomicrograph of the first part of the duodenum in a 42 mm. guinea pig embryo (×37). Note common bile duct (*D. chol.*) in duodenohepatic ligament (*Mesent.*) and subdivision of the ampulla of Vater into an ampulla proper (the antrum of Westphal) and a duct of the ampulla (*D. amp.*), lying in the papilla (*Pap.*). Since this is an oblique section, the circular layer of the duodenum (*T. musc.*) is cut somewhat transversely. *The vestige of a vacuolated epithelium which completely filled the lumen of the intestine in earlier stages. The establishment of an intestinal lumen is a much slower process in the guinea pig than in the human embryo. For lower levels in the same specimen, see Figs. 3 and 4.

*Apparently, however, the expelling mechanism of the opossum represents but a vestige of that which exists in fishes, for Higgins[23] has shown that in the common bullhead, peristaltic waves begin in the fundus of the gallbladder and extend all the way down the biliary tract into the duodenum. Furthermore, in its course through the intestinal wall, the somewhat thickened muscle of the bile duct is separated from the muscle of the intestine by a wide connective tissue layer (Fig. 9, loc. cit.). Since the intramural coat is merely a continuation of that around the extramural portion of the duct, Higgins raises the question as to whether it should be designated "sphincter of Oddi." I would reply that very likely this purely biliary muscle represents the first stage in the differentiation of the sphincter and that Dr. Higgins' important observations have provided the first clue to the phylogenetic origin of a structure which may have arisen as a compensation for loss of peristalsis in the upper regions of the biliary tract.

when the musculus proprius develops, it blends with the intestinal tunics (cf. Figs. 2-4). Undoubtedly, also, its presence there, from the beginning, has modified the growth of the intestinal muscle. This blending of layers, however, does not occur in such animals as the cat where the ampulla lies in the submucosa and pancreatic and bile ducts occupy the level of the window. In such species the intestinal muscle may enter into complicated relationship with the two ducts, but the musculus proprius can be differentiated as a separate layer. The guinea pig, therefore, presents the most intimate union between biliary and intestinal musculature.

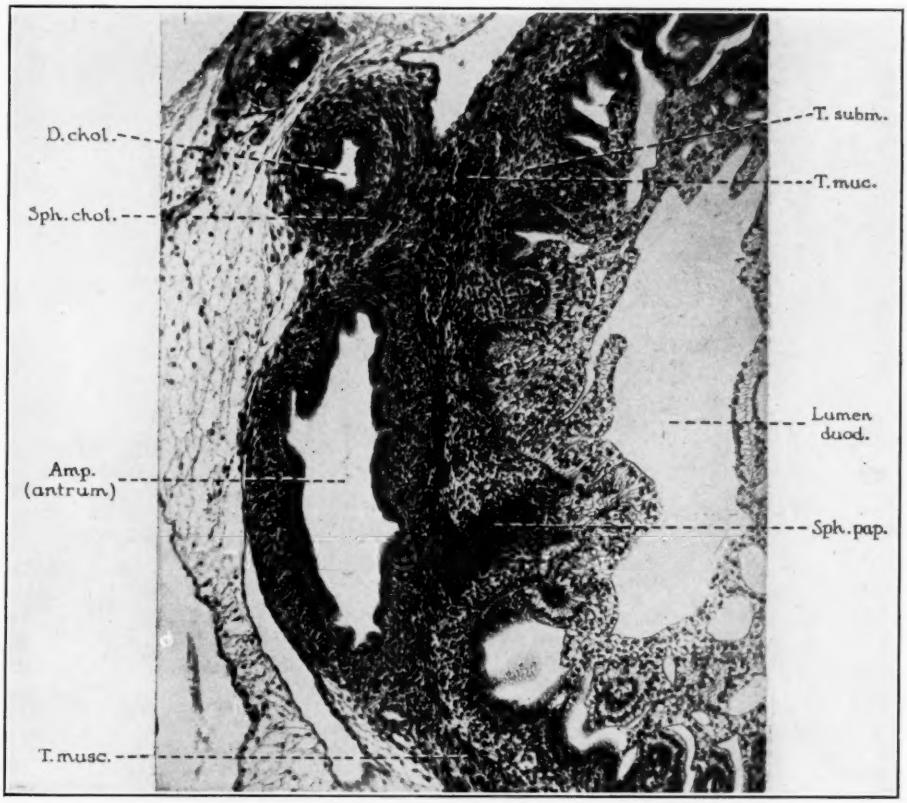

Fig. 3.—Photomicrograph of the same duodenum as that shown in Fig. 2, seven sections lower down (×90). Note sphincter around common bile duct (*Sph. chol.*) and tangential section of sphincter around the duct of the ampulla (*Sph. pap.*). The embryo is too young for the layers of muscle around the ampulla to be fully differentiated but longitudinal fibers can be seen leaving the mucosal side of the transversely cut intestinal muscle layer (*T. musc.*). (Cf. Fig. 1, guinea pig.)

Nevertheless, Higgins[16] has noted that while peristalsis of the duodenum may affect the ampulla, active pulsations of the pouch can be observed in the absence of intestinal peristalsis. Furthermore, DuBois and Kistler[24] have shown that faradic stimulation of the antrum induces marked contraction of the gallbladder and that this effect disappears when the bile duct is severed; from these facts they infer the existence of a direct nervous pathway from ampulla to gallbladder.

Finally, mention must be made of the musculus proprius of the *duct* of the ampulla to which Westphal[6] has given the name sphincter papillae (cf. Figs. 1 and 3). He compares this to the pyloric sphincter and likens the ampulla to the pyloric antrum of the stomach, finding that the two sphincters are excited by the sympathetic system and that the two antra are caused to undergo peristalsis or even spastic contraction, by the vagus nerve.

In man, the muscle of the ampulla is a relatively weak layer, some distance removed from the intestinal window, and consists of lateral

Fig. 4.—Photomicrograph of the same duodenum twenty sections below the level shown in Fig. 3 (×90). This shows the ampulla cut obliquely lengthwise and bulging from the intestinal wall into the mesentery, below the level at which it has been joined by the common bile duct.

bundles of longitudinal fibers overlying an inner circular layer (Fig. 5). No differentiation of this sheath into ampullary zone and sphincter papillae is demonstrable; nor do these layers seem strong enough or complete enough to provide a mechanism for peristalsis. It is believed, therefore, that the longitudinal fibers act in shortening the ampulla and that the circular fibers are chiefly effective in regulating the flow of pancreatic juice (described later).

In the dog, there is no ampulla of Vater and therefore no musculus proprius ampullae, unless the few delicate terminal rings that encircle both bile and pancreatic ducts just before they empty into the duodenum (Figs. 1 and 6) may be considered as such.

THE SPHINCTER CHOLEDOCHUS

In the opossum, the bile and pancreatic ducts, throughout the zone in which they run parallel to each other, are enveloped by a common sheath of intrinsic muscle which consists of well-developed outer circular and inner longitudinal layers (Fig. 1). This sheath is an upward extension of the ampullary musculature. In addition, the bile duct itself, above the point where it comes in contact with the pancreatic duct, has a double sheath for a short distance—the musculus proprius ductus choledochi. Its thin, outer, circular layer might be called a potential sphincter choledochus, since increase in tone would compress this segment of the duct, but DuBois and Hunt have never seen it contract independently of peristalsis.

In the guinea pig, however, there is a most powerful sphincter at this point. It has been observed in the living both by Higgins[16] and by Burget and Brocklehurst.[17] As peristaltic waves pass down over the bile duct onto the antrum, this sphincter contracts to prevent regurgitation of bile toward the liver.

In man there is a corresponding musculus proprius of the bile duct which begins just outside the intestinal window and extends to the ampulla (Fig. 1). Circular fibers predominate throughout, and these reach their greatest thickness near the ampulla. They are the "*IR*" and upper "*S*" fibers of Hendrickson.[25] This zone Dr. Schwegler and I have named the *sphincter choledochus*, and we consider it the most important part of the human sphincter of Oddi. A transverse section of it, in a seven months' fetus, is shown in Fig. 5. Our embryologic studies indicate that it is entirely independent of the intestinal musculature, arising in situ from mesenchyma, like the musculus proprius of the ureter. Apparently it is the only zone capable of retaining the column of bile. Its importance has also been stressed by Matsuno,[26] who considered this band thick enough to produce biliary stasis. Incidentally, Nuboer[4] has published sections showing the hypertrophy of this zone in an eighty-three-year-old patient in whom the gallbladder had been sidetracked by cholelithiasis. On the physiologic side Ivy, Voegtlin, and Greengard[27] have provided striking evidence that the column of bile can be held in the presence of an abundant flow of pancreatic juice. Having injected a human subject intravenously with 300 dog doses of secretion and 10 dog doses of cholecystokinin, they aspirated 162.5 c.c. of pancreatic fluid in forty-nine minutes. But this flow was

accompanied by typical gallbladder distress, which increased steadily until the pain was unbearable. At the end of forty-nine minutes a concentrated solution of magnesium sulphate was given by tube. In two minutes the distress disappeared and in seven minutes typical gallbladder bile was aspirated, showing that the salt had relaxed the sphincter that was holding the column of bile while the pancreatic juice was flowing.

In the dog[21] almost the entire intramural course of the bile duct is encircled by scattered loops of intrinsic muscle. The lowest of these

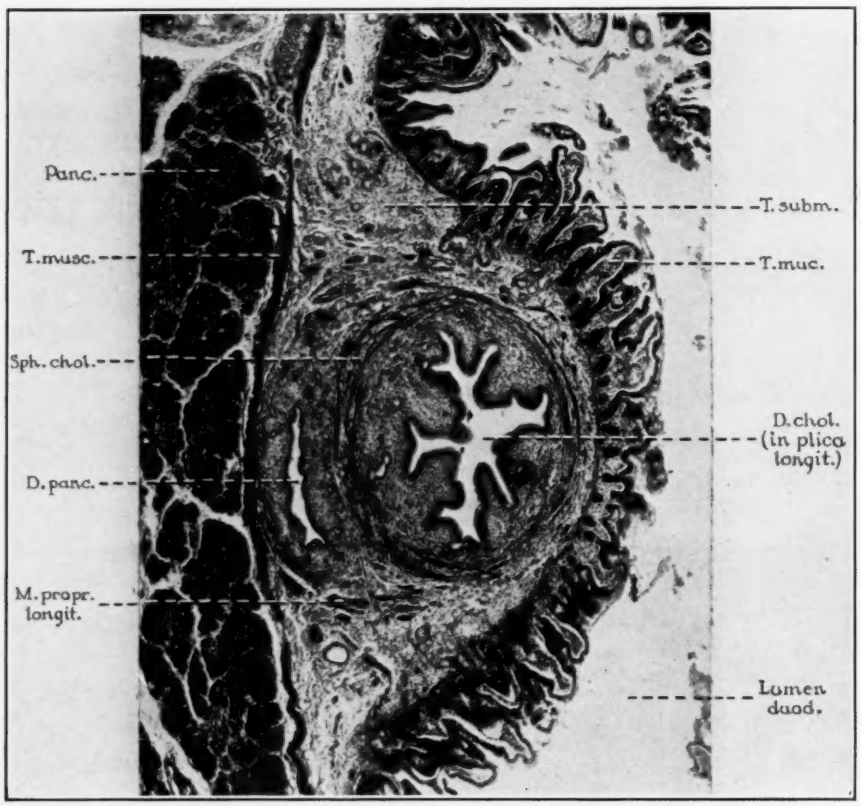

Fig. 5.—Photomicrograph of transverse section of pars intestinalis of common bile duct in a seven months' human fetus (from the studies of Schwegler and Boyden). (×34.) Note that the bile duct in its transit through the submucosa is surrounded by a thick ring of smooth muscle (*Sph. chol.*) which is some distance removed from the muscle of the intestine (*T. musc.*). No muscle ring surrounds the pancreatic duct (*D. panc.*), but there are longitudinal fibers (*M. propr. longit.*) which correspond to the "H," "K," and "X" fibers of Hendrickson (1898). This section lies a short distance above the level where bile and pancreatic ducts unite to form the ampulla of Vater (Fig. 1).

loops is thicker and more isolated than the rest and may be called the subterminal portion of the sphincter choledochus or the subterminal ring (annulus subterminalis; Figs. 1 and 6). Judging from the experiments of Lueth[28] it plays an important rôle in retaining the bile. This author noted that when a cannula was advanced through the

intramural portion of the bile duct, the pressure fell in steps, and the distal zone bulged before the orifice opened, thus implying muscular compression near the end of the duct.

THE SPHINCTER PANCREATICUS

This is the least developed of all the intrinsic musculature under discussion. In the opossum it is barely suggested by tenuous strands (not shown in Fig. 1), which partially encircle the pancreatic duct in

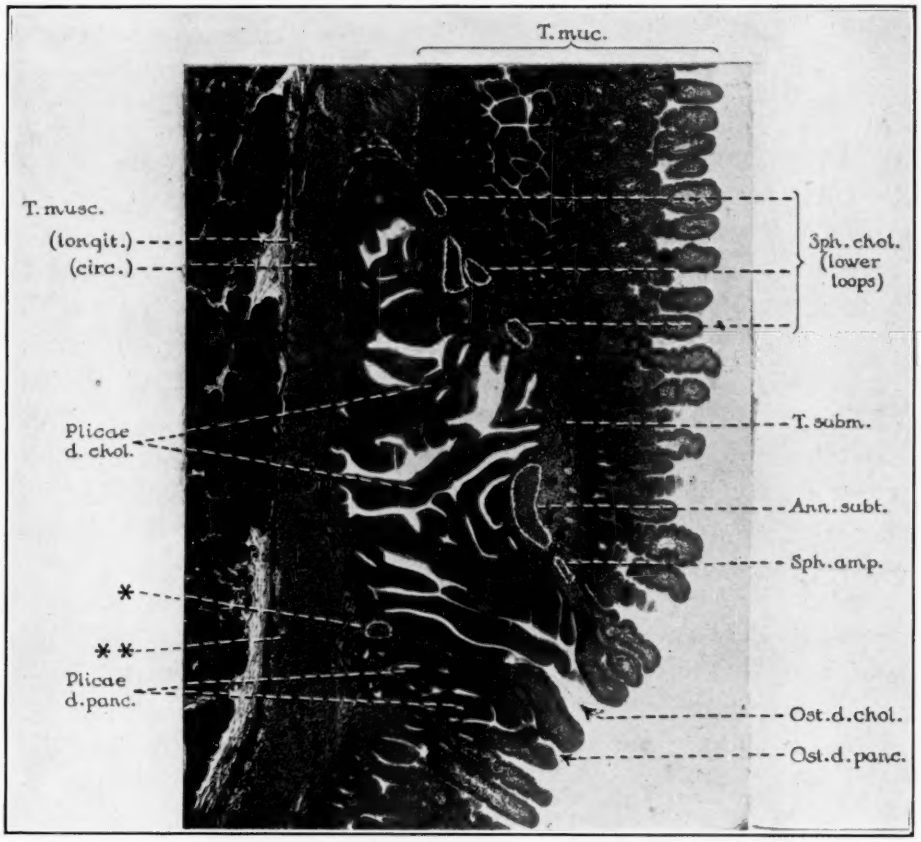

Fig. 6.—Photomicrograph of lower third of intramural course of bile duct in a newborn puppy, cut almost longitudinally (×37). In this section the lower loops of the sphincter choledochus (Fig. 1, dog) are cut transversely, and their margins have been outlined in white, since unfortunately the azocarmine stain which separates muscle from connective tissue so clearly does not photograph well. The lowest of these loops around the bile duct is the subterminal ring (*Ann. subt.*). Still nearer the lumen of the intestine and surrounding the orifices of both the duct of Wirsung (*Ost. d. panc.*) and the bile duct (*Ost. d. chol.*) is a vestige of the sphincter ampullae (*Sph. amp.*); *, portion of intrinsic muscle common to both the pancreatic and the subterminal sphincter (Fig. 1, dog); **, point at which the pancreatic duct will penetrate the circular muscle layer of the duodenum.

the region where the bile and pancreatic ducts first approach each other. Obviously, compression of the pancreatic duct is accomplished primarily through the layer of circular muscle which is common to both bile and pancreatic ducts. Apparently the same holds true in

man, for Schwegler and I have found no muscle fibers which completely encircle the pancreatic duct in the human fetus (see Fig. 5).

In the dog, however, where the duct of Wirsung empties separately into the duodenum, there is a ring of muscle which tends to form a figure eight with the subterminal portion of the sphincter choledochus (Figs. 1 and 6). This has previously been noted by Hendrickson. It may be considered a true sphincter pancreaticus. For this reason we cannot follow Hendrickson in homologizing it with the fibers that constitute the sphincter choledochus.

DISCUSSION

Obviously, in this short article, it has been impossible to present any detailed description of these four species—a task which necessarily has been left for subsequent publications; rather, the object has been to give a general picture of the sphincter and to provide an anatomic foundation for analyzing its behavior in different species. To suggest how much such information is needed one has only to turn to Aschoff's much publicized diagram of the human biliary tract (Fig. 7) which, incidentally, is the best available. Here we see the terminal portion of the bile channel divided into two successive zones on the basis of Westphal's experimental study of the guinea pig and rabbit. The upper segment which represents the zone of the bile duct and its sphincter is labelled "antrum," yet the "antrum" of the guinea pig is the ampulla of Vater. The lower segment (the zone of the ampulla) is called "sphincter papillae," i.e., the muscle which in the guinea pig surrounds the *duct* of the ampulla. Whether these two regions in the guinea pig and man react to the same stimuli remains to be proved, but in any case they cannot logically be given the same name.

A second matter with which it has been impossible to deal, in the limits of this paper, is the disposition of intestinal muscle around the bile ducts. In general, however, the species differences in the pattern of this muscle are as marked as those in the intrinsic musculature. Two points only will be mentioned. In man, the window in the duodenal muscle, through which bile and pancreatic ducts enter the intestine, is of such shape and size that duodenal peristalsis exerts a minimal effect on the flow of bile. This may afford one explanation for the fact that in man two-thirds to three-quarters of the contents of the gallbladder are emptied within the first forty minutes after a meal of egg yolk.[29, 30] By contrast the duodenal window of the dog has the shape of a funnel which envelops the first two-fifths of the intramural course of the bile duct. This may account for the fact that the phases of emptying in the dog are short and intermittent (lasting

for only a few minutes, as pointed out by McMaster and Elman),[31] and that therefore the gallbladder of this species is sluggish and rarely evacuates itself completely. Physiologic confirmation of this is to be found in the experiments of Sandblom, Voegtlin and Ivy.[32] Employing dogs in which devices for securing simultaneous records of pressure changes in the duodenum and common duct had been installed, these authors found that intravenous injections of cholecystokinin increased duodenal tone and motility in 87 per cent of cases—although in the few instances in which the action of the drug on the sphincter of Oddi was not masked the sphincter was relaxed by the drug—thus emphasizing the obstructive effect of duodenal tone and motility in the dog.

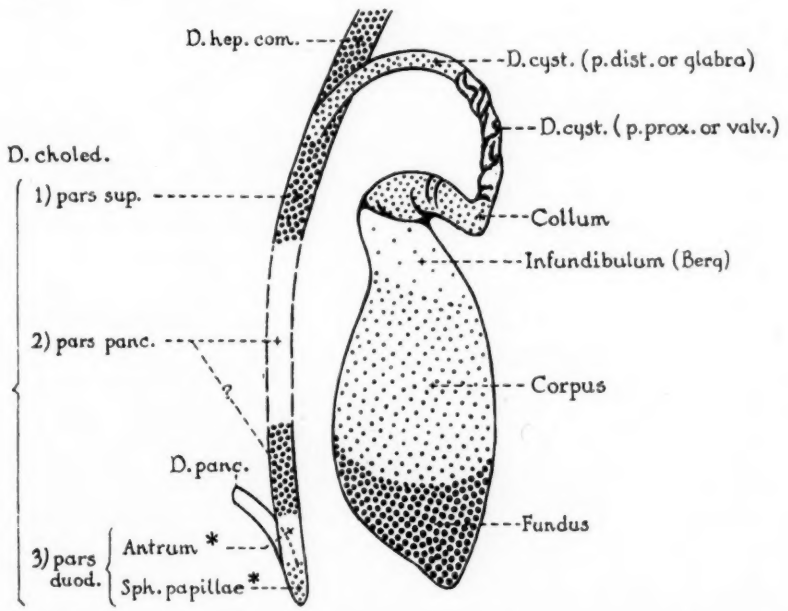

Fig. 7.—Aschoff's diagram of the extrahepatic bile passages in man (posterior view), to which has been added the ductus pancreaticus. (From Arch. f. klin. Chir. 126: 233, 1923.) This diagram is based largely on Charpy's account of the biliary tract in Poirier and Charpy's Traité d'Anatomie Humaine, 1901. *Westphal's names for upper and lower segments of the pars intestinalis in the guinea pig and rabbit. In man these portions of the musculus proprius should be called respectively, the sphincter choledochus and the sphincter ampullae.

SUMMARY

In conclusion, it may be noted that comparative embryologic studies have demonstrated that in the opossum, guinea pig, dog, and man, the pars intestinalis of the bile channel (and its associated duct of Wirsung, if present) is ensheathed in a two-layered musculus proprius which can be designated, legitimately, the sphincter of Oddi. The four species differ markedly in the degree to which different segments of the sheath are developed or suppressed, and in the relationship they bear to the duodenal muscle through which the bile duct enters the

intestinal wall. The human sphincter has three marked anatomic characteristics: (1) its relative freedom from intestinal interference, due to the configuration of the window in the duodenal muscle through which it passes; (2) the retrogression of its ampullary segment; and (3) the development of a special constricting mechanism (the sphincter choledochus) just above the point where the bile duct joins the ampulla of Vater. Anatomically, this zone of intrinsic muscle would seem to be entirely adequate to sustain the column of bile and so to cause the gallbladder to fill during the interval between meals. If such be its normal function, it is not difficult to believe that hypertrophy or overstimulation of so strategically a placed sphincter would result in biliary stasis and the production of right hypochondrial distress.

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THE FUNCTION OF THE "VALVES" OF HEISTER

MANUEL E. LICHTENSTEIN, M.S., M.D., AND A. C. IVY, PH.D., M.D.,
EVANSTON, ILL.
(From the Department of Physiology, Northwestern University Medical School)

INTRODUCTION

ALTHOUGH the "valves"* in the cystic duct were well described and illustrated by Heister in his textbook,[1] he had difficulty in convincing others that these folds actually existed (Fig. 1). Subsequent observers, however, confirmed his findings and added much speculation concerning their function. They have been studied from many points of view, and considerable information concerning their anatomy, embryology, physiology, and pathology has been recorded.

On the basis of this work, various views of the function of the "valves" of Heister have been expressed. Some have suggested that their function is to impede the inflow of bile into the gallbladder,[2] while others have suggested that they impede[3] or prevent[4] the outflow of bile from the gallbladder. Keith[5] has suggested that they prevent collapse by providing support to the walls of the duct. They have been viewed as baffle plates[6] to secure a slow passage of viscous bile from the bladder without opposing the flow of thin hepatic bile into the gallbladder. Studies have been made on the pressure required to force fluid through the cystic duct in either direction. Lohner[7] observed that less pressure is required to cause fluid to flow into the gallbladder than out of it. Mentzer[8] concluded that the "valves" of Heister check the rapid passage of fluid into or out of the gallbladder. Johnson and Brown[9] found no real impediment to the passage of fluid into or out of the gallbladder when the pressures found normally in the gallbladder were used. At lower pressures (8 cm. of water or below), a lag in the equalization of pressure between the gallbladder and the common duct was observed. This was attributed to the size of the ducts or to a "suction" action collapsing the ducts. The same authors also observed that the pressures between the duct and gallbladder equalized almost instantly and tended to do so even at low pressures. This held true when the pressure was varied on either side of the cystic duct.

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*The term "valves," referring to the folds in the cystic duct described by Heister, is retained for its historical interest. The folds, in fact, are not valves but are referred to as such in the same sense that the projections into the lumen of the small intestine are called "valvulae conniventes."

Thus, while many suggestions have been offered, the question of the function of the "valves" themselves still remains unanswered. If they are not a factor in regulating the flow of bile into or out of the gallbladder, the variations of rate of flow under varying pressure changes noted by Lohner, and Johnson and Brown require an explanation. The suggestion of Keith that they prevent collapse of the cystic duct is interesting, but further study seems indicated before it can be accepted.

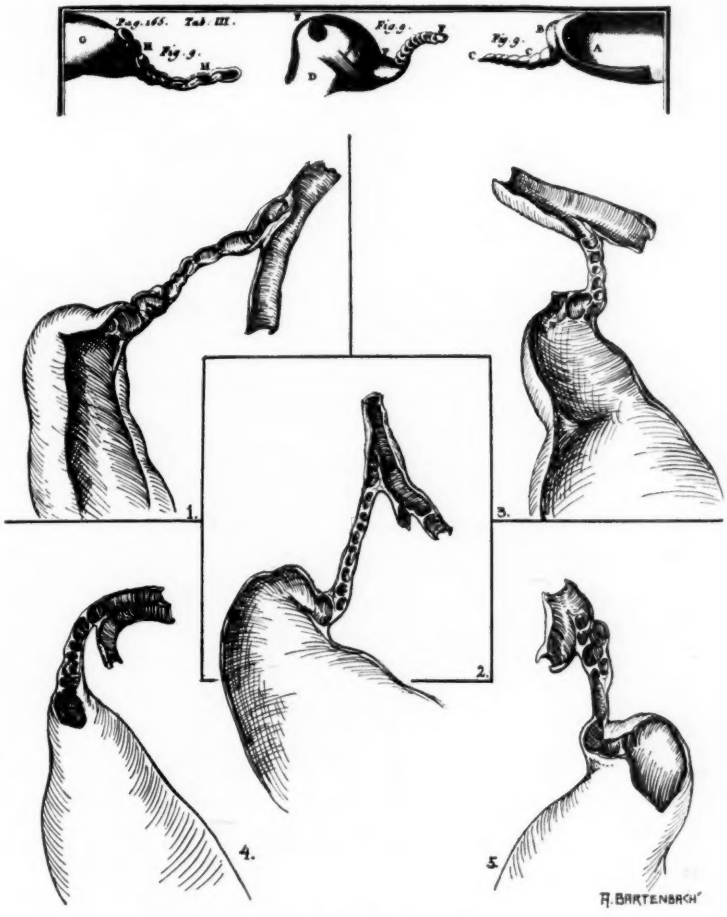

Fig. 1.—The "valves" of Heister.

ANATOMY

The "valves" of Heister are located in the neck and duct of the gallbladder. The anatomical divisions of the gallbladder are illustrated in Fig. 2.

The neck is defined[10] as that portion between the first "valve" of Heister and the beginning of the cystic duct. This portion is usually demarcated proximately by a bend which appears between the infundibulum and neck, and distally by a bend between the neck and

cystic duct. The neck is usually fixed to the infundibulum rather loosely by areolar tissue surrounded by a fold of peritoneum. It is difficult, however, to separate the neck from the infundibulum when the cystic artery is intact, as the latter crosses both of these portions of the gallbladder and fixes them to each other. The neck varies considerably in size and shape and in many instances is not well defined.

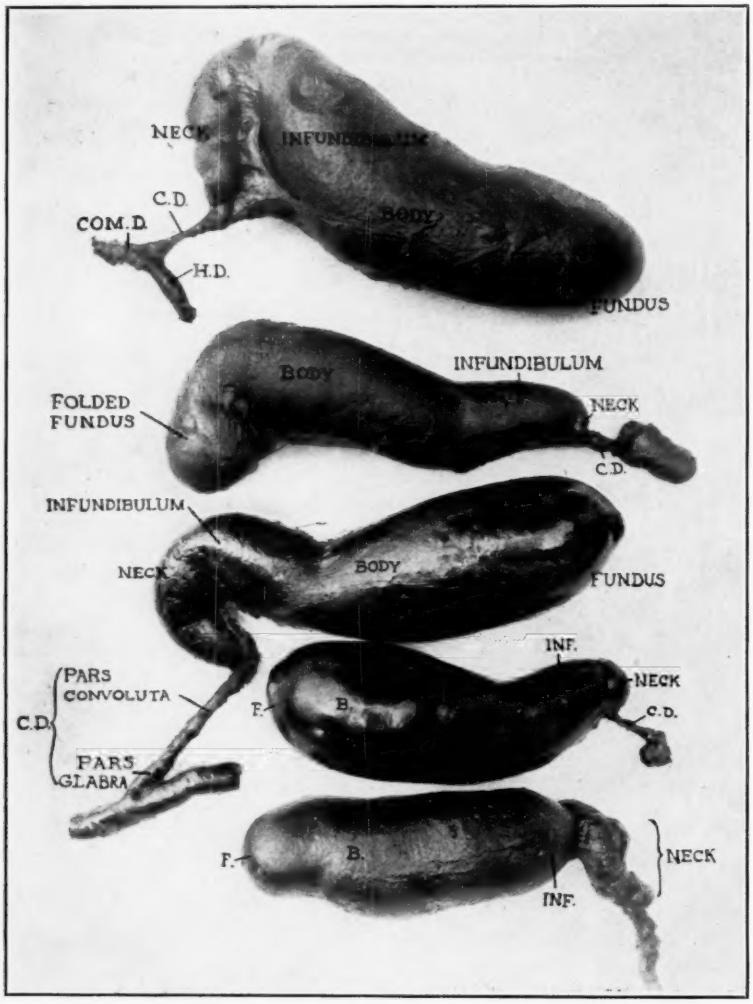

Fig. 2.—Anatomical divisions of the gallbladder.

The neck may continue imperceptibly into the cystic duct without a distal demarcation. It may be limited at either end by a single valve, or it may have a well-defined spiral fold extending the full length of its lumen. In some instances the first "valve of Heister" does not appear to be an independent leaflet projecting into the lumen of the gallbladder (Fig. 3*A*). We found that it may be made to disappear by removing all areolar tissue connections between the infundibulum

and neck and by then straightening the organ. This is similar to the fold that appears in the "folded fundus"[11, 12] (Fig. 3*B*), and the origin may be identical.

The cystic duct varies in length, diameter, shape, configuration, internal architecture, and relation to surrounding structures (Fig. 4). The mucous membrane surface in many instances is divided into two distinct portions—the proximal portion with projections ("valves") called the pars convoluta and a distal portion without projections called the pars glabra. When the cystic duct is fully distended by air or water, it is found that the caliber of the pars convoluta is usually less than that of the pars glabra (Fig. 5).

At the junction of the cystic and the common hepatic ducts, a leaflike fold is present. This projects toward the distal portion of the

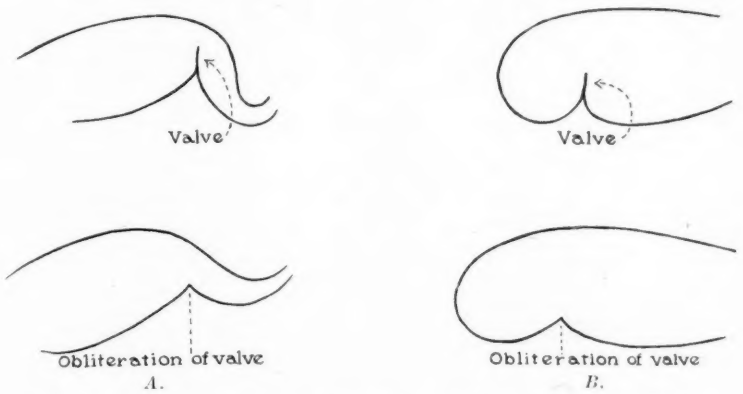

Fig. 3.—Leaflike projections in neck and fundus of gallbladder.

common duct, and it is likely that it acts as a wing dam deflecting the flow of bile away from the opening of the cystic duct (Fig. 6). If obstruction should occur, however, in the common duct distal to the entrance of the cystic duct, as occurs with the contraction of the sphincter of Oddi, or increase in tone of the duodenal musculature, bile would then back up into the cystic duct and enter the gallbladder. Thus, on the basis of anatomical structure, the filling of the gallbladder is dependent on an increase in pressure in the common duct due to closure of the outlet of the latter.

The adherence of the terminal part of the cystic duct to the common hepatic duct is of surgical importance. Numerous cases have been reported in which the latter was injured during operation or mistaken for the cystic duct and ligatured. These accidents are most likely to occur when the gallbladder is distended and the liver is in normal position, because the neck projects medially upward between the layers of the hepatoduodenal ligament and lies in contact with the common hepatic duct, the entire cystic duct being adherent to the latter.

Practically all forms of liver displacement tend to straighten out the cystic duct, but marked ptosis may produce a very acute bend in the cystic duct near its junction with the common hepatic duct, thus favoring obstruction.

Adhesions may fix the gallbladder to adjacent viscera, or by traction prevent the outward displacement of the gallbladder, or produce

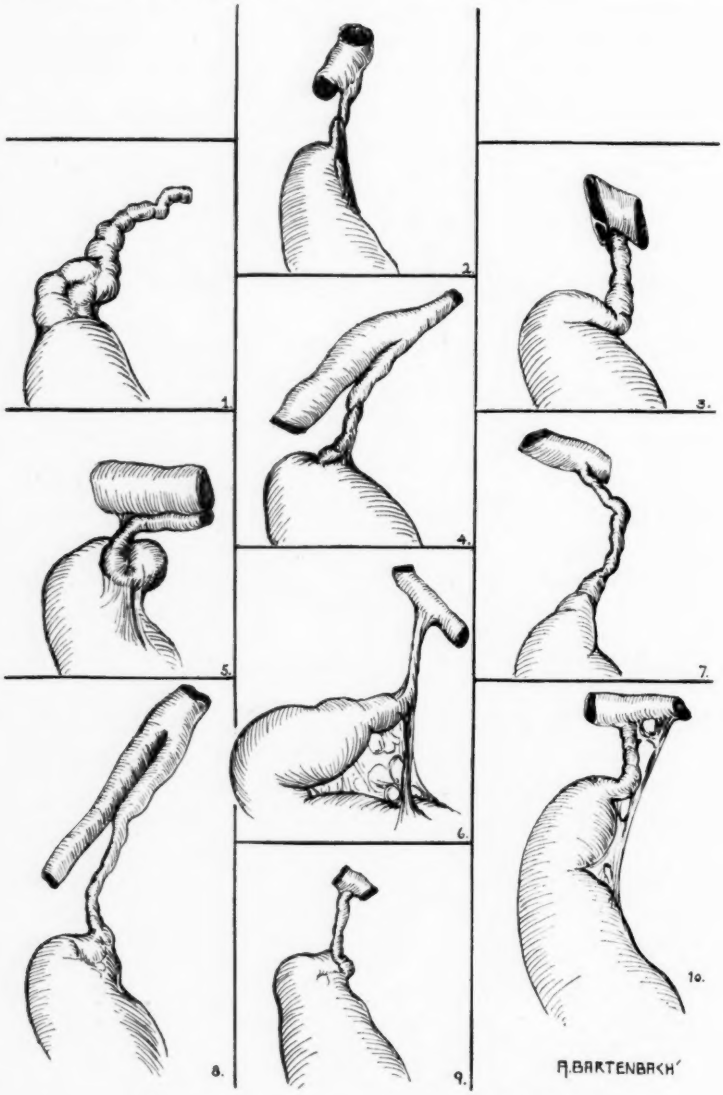

Fig. 4.—Variations in shape of cystic duct.

a downward displacement of the body of the gallbladder with angulation at the neck and duct.

Observations on the size, form variations, modes of union of the cystic duct with the common hepatic duct, and the relations of the cystic artery are of interest (Table I).

TABLE I

I. LENGTHS OF NECK AND DUCT OF GALLBLADDER

CM.	NECK	CYSTIC DUCT
0-1	2	1
1-2	22	19
2-3	16	28
3-4	7	27
4-5	2	12
5-6	0	7
6-7	1	3
7-8	0	2
8-9	0	0
9-10	0	1
No. of specimens	50	100

55 per cent of cystic ducts are between 2 and 4 cm. in length
20 per cent of cystic ducts are less than 2 cm. long
25 per cent of cystic ducts are more than 4 cm. long

II. CIRCUMFERENCE VARIES BETWEEN 4 AND 10 MM.
AVERAGE CIRCUMFERENCE IS 6 MM.

III. FORM VARIATIONS:
Spiral
Kinked
Constrictions
Knots
Tortuous

IV. CYSTIC DUCT UNITES WITH HEPATIC DUCT:[15]

Angular	(292 in 389 instances)
Parallel	(64 in 389 instances)
Spiral	(67 in 626 instances)

From evidence submitted by Boyden[13] and Rietz,[14] it appears that the peculiar conformation of the cystic duct and neck of the gallbladder is due to the accommodation of a rapidly growing tube in the slower growing mesenchymal bed of the gallbladder (Fig. 7). Since the bed limits the extent of growth, the gallbladder develops folds and twists which are more exaggerated at the neck and cystic duct. Further limitation of longitudinal growth occurs here, because the cystic artery fixes the space available for the neck and cystic duct.

There is much to support this view. The folds which appear in the lumen of the duct and neck of the gallbladder appear to be more marked in the young and tend to be more flattened in the old. In the embryo, a spiral-like "valve" is present, but this spiral partly disappears in the adult or is flattened so that only segments are left which are connected by newly developed small folds in the mucous membrane. The valves or folds are most discernible in that portion of the duct close to the neck of the gallbladder and decrease in number in the more distal portion of the cystic duct. It is rare to find "valves" in the distal portions of exceedingly long cystic ducts, but it is common to find them throughout the whole extent of short ducts. It must be understood, too, that folds may appear in the body of the gallbladder (folded fundus, folded body) and for the same reason. Examination

of the mucous membrane projections into the lumen of the gallbladder shows that these folds are similar to the folds of the cystic duct associated with the "valves." Where large folds have occurred, these may be straightened with disappearance of the "valve" in the interior of the gallbladder (Fig. 3).

This embryologic origin of the "valvular" folds also accounts for the variable number of folds from complete absence to as many as twenty and accounts for the peculiar twists, knots, kinks, spirals, and

Fig. 5.—The cystic duct. Note that the pars glabra is wider in diameter than the pars convoluta.

other formations which tend to show an effort was made to accommodate a long tube in a limited space. Since gallbladders vary in size and the liver beds also vary in size, the extent of folding in each individual case will depend on the relationship between the developing gallbladder and its mesodermal bed.

PHYLOGENY

It is of interest to note that phylogenetically the "valves" of Heister appear only in primates. It is possible that the assumption of the erect

posture has limited the space in the upper abdomen for accommodation of the liver. Also, the development of folds and ligaments, such as

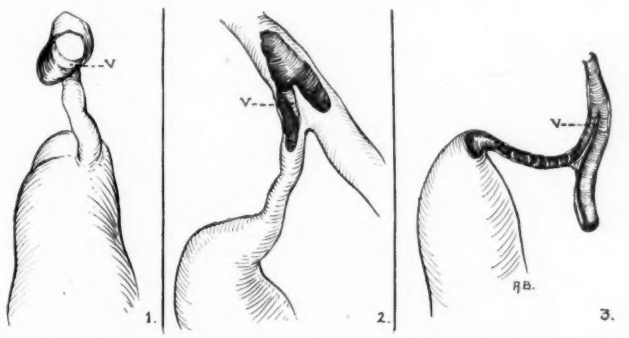

Fig. 6.—At "V" is the small leaflike process which appears to arise by the fusion of the walls of the cystic and hepatic ducts.

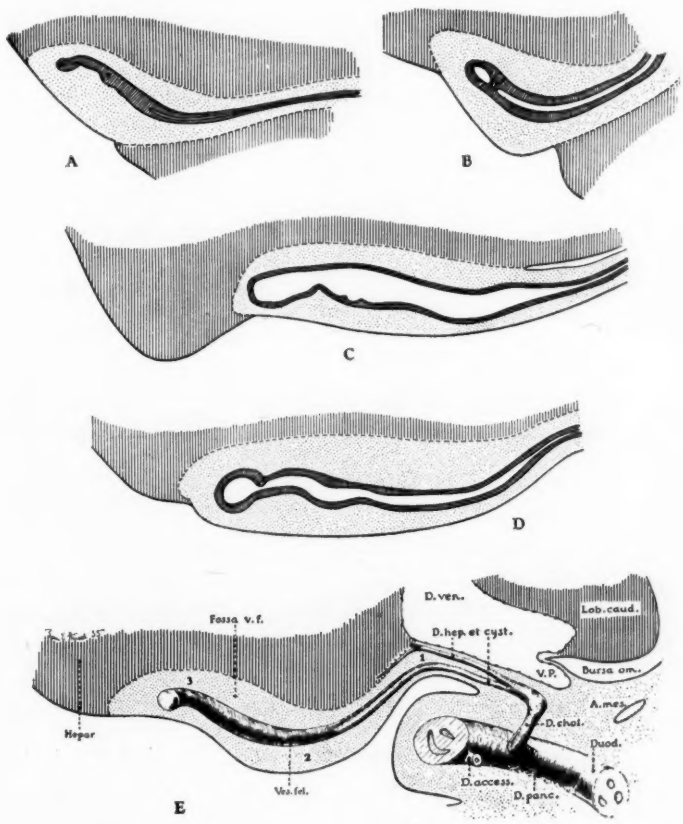

Fig. 7.—From Boyden.[13] Stages in the development of the gallbladder. In *E* note the three sites (1, 2 and 3) at which bends may occur.

Keith and Lane have described, to fix the viscera in the upright position may have been responsible for the twisting of the cystic duct, which resulted in the formation of the "valves."

It is difficult to correlate the size of the liver or the number of lobes of the liver with the station of the species in the mammalian scale. In general the liver in man is smaller, however, in proportion to the size of the body, than in any species except that of the goat and horse.

METHOD OF INVESTIGATION

I. Specimens of human gallbladders with their attached ducts (cystic, hepatic, and common) were obtained at autopsy within twelve to twenty-four hours after death. The cystic artery, which attached the body to the neck of the gallbladder in such a manner as to preserve the bend at their junction, was left intact. The hepatic duct was

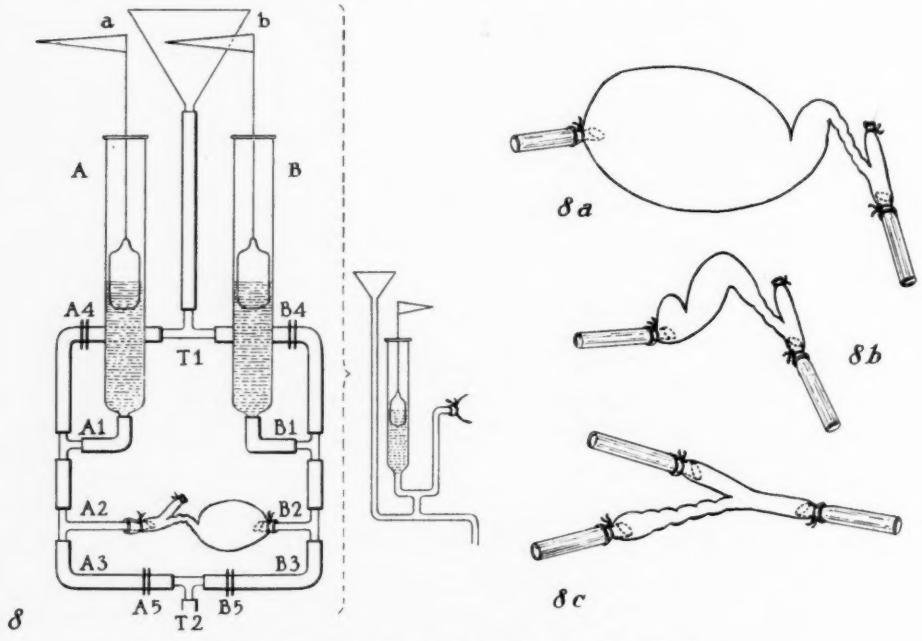

Fig. 8.—Apparatus and types of preparations.

ligated. The common duct and fundus of the gallbladder were cannulated and attached as indicated in Fig. 8*a*. The cannulas had a diameter that approximated that of the cystic duct.

Salt solution (0.9 per cent) passes from the funnel into the arms *A* and *B* of a T-tube, *T 1* (Fig. 8). It is then carried to *A 1* and *B 1*, which are connected with a water manometer having floats, *a* and *b;* and to *A 2* and *B 2*, which are attached to cannulas in the gallbladder and common duct; to *A 3* and *B 3*, which lead into a flask through a common tube, *T 2*. Clamps are placed at *A 4*, *B 4*, *A 5*, and *B 5*. The pressure in the gallbladder may be elevated by opening the clamp at *B 4*. This pressure may be recorded on a smoked drum by the float, *b*. The pressure may be decreased in the gallbladder by opening the clamp,

B 5. Likewise, the pressure in the common duct may be elevated by opening the clamp, *A 4,* and it may be decreased by opening the clamp, *A 5.*

II. In some instances the body of the gallbladder was removed, and the cannula was placed into the infundibulum with its orifice facing the beginning of the neck. This was proximal to the first bend and also to the first Heister valve (Fig. 8*b*).

III. To determine more accurately the effect of the presence of the valves of Heister on the flow of fluids through the cystic duct, the apparatus was arranged as in Fig. 8*c*. In these experiments only the straight portion of the cystic duct was used. The cannula was placed into the neck of the gallbladder so that the orifice of the cannula just entered the straight part of the duct. The cannulas in the hepatic and common ducts were so placed that they did not interfere with the passage of fluid into the orifice at the termination of the cystic duct.

The ducts were placed on a level plane in line with the 0 mark on the manometers. The three locations of the cannulas on the gallbladder side of the cystic duct were associated with slightly different results.

RESULTS

I. Using several methods of observing the flow of fluids through the cystic duct with the gallbladder intact, it was found that the results were approximately similar to those following the use of the apparatus illustrated. With high pressures (over 15 cm. of solution), equalization of pressure takes place promptly. The ducts are dilated, the neck of the gallbladder stands erect, and there is no obstacle to the passage of fluid through the cystic duct in either direction. With lower pressures, equalization occurs on both sides of the cystic duct, but there remains a slightly higher pressure on the side of active flow. When fluid passes into the gallbladder, the pressure in the common duct is slightly higher than that in the gallbladder. Likewise, when fluid passes into the common duct, the pressure is slightly higher in the gallbladder. These results confirm the findings of Johnson and Brown.

II. Using the second type of preparation in which the body of the gallbladder is removed (Fig. 8*b*), the following differences in results were noted as compared to the first type (Fig. 8*a*) of preparation:

1. No filling of the gallbladder was necessary, hence the rise in pressure occurred almost immediately on the opposite side of the cystic duct.

2. At approximately 5 cm. pressure, equalization in pressure occurred promptly. At 2 to 3 cm. pressure or lower, a lag in equalization was noted.

III. Using the "setup" shown in Fig. 8*c*, equalization of pressures on either side of the cystic duct was immediate, with pressures varying from 3 mm. to 200 mm. 0.9 per cent NaCl. The sizes of the ducts are recorded in Table II.

TABLE II

SIZE OF CYSTIC DUCT IN CM.

LENGTH	CIRCUM.	"VALVES"
1.5	0.5	4
2.6	0.8	6
3.0	0.6	2
3.4	0.6	4
3.8	0.8	6
4.0	0.6	6
4.0	0.4	5
4.5	0.8	4
4.5	0.6	12
4.8	0.8	7
5.0	0.8	6
5.4	0.8	8
6.4	1.0	4
7.5	0.8	9

SUMMARY OF RESULTS

With the gallbladder intact, an adequate volume of fluid is required to fill the gallbladder before any of it will pass into the cystic duct. The gallbladder must be well filled before sufficient pressure may be attained to force fluid through the neck and cystic duct and to have the fluid appear on the common duct side. When stabilization of fluid levels occurs, it has been found that there remains a residual slightly higher pressure on the gallbladder side than on the common duct side. This amounts to from 0.5 to 3.0 cm. of pressure. Also, when fluid passes from the common duct through the cystic duct and neck of the gallbladder, equalization of pressures to the point of stabilization shows a slightly higher pressure on the common duct side than on the gallbladder side.

These findings are in accord with those of Johnson and Brown. When the second type of preparation was used (body of gallbladder removed), the flow through the tubes was more prompt, but there still remained a slight residual pressure on either side, which was higher than on the opposite side, this higher pressure being on the side of active flow from the funnel.

When the third type of preparation was used, even at the slightest pressure of 1.0 to 3.0 mm. of water, prompt equalization of pressure occurred. These findings were found in specimens that had few (2), as well as many (up to 12), "valvular" projections into the lumen of the cystic duct. Also, this was true, regardless of the size and degree of tortuosity of the cystic duct.

DISCUSSION

From these findings it would appear that the "valves" themselves offer no resistance to the passage of fluids in either direction, that the bends at the junctions of the neck with the gallbladder on one side and the cystic duct on the other offer a slight degree of resistance to the flow of fluid both into and out of the gallbladder, and that when the pressure in the gallbladder is sufficient to cause a straightening of the neck, fluid will pass unobstructed out of the gallbladder. As is well known, it is rare to find an empty gallbladder. This may be due to the necessity of having an appreciable pressure, though small, to maintain a patent passage between the gallbladder and cystic duct.

When one observes formalin hardened specimens of cystic ducts which have been cut open longitudinally, one finds that the direction of the pockets formed by these leaflets faces in some instances toward the common duct, as though to impede the entrance of material into the gallbladder, while in other instances it faces toward the neck of the gallbladder. Yet dark, thick bile obtained from the gallbladder and poured into a cannula attached to the common duct will flow into the gallbladder under a pressure of 2 to 3 cm. of bile pressure. How much of this 2 to 3 cm. pressure is due to the resistance of the caliber of the tube could not be determined. As the hepatic bile is much thinner than gallbladder bile, it is not likely that the "valves" offer any resistance to the flow of bile into the gallbladder.

That some should suggest impediment of outflow of bile from the gallbladder is likely from the fact that gallbladder bile is more viscous than hepatic bile and must pass through the narrowest portion of the extra hepatic biliary passages, whose lumen is further limited in size by the presence of the "valves." The facts are, however, that gallbladder bile is able to pass through the cystic duct and empty into the more commodious common duct.

The presence of valves in the cystic duct does not seem to impair the passage of 0.9 per cent sodium chloride solution, or tap water, or gallbladder bile in either direction.

It has been suggested that the valves act as baffle plates to permit inflow and outflow simultaneously. This does not appear likely, as the inflow of bile into the gallbladder is dependent upon an increase in tone of the sphincter of Oddi. This results in an increase in the pressure in the common duct with opening of the orifice at the entrance of the cystic duct into the common duct.

When the sphincter of Oddi is relaxed, hepatic bile will flow directly into the duodenum. The only manner in which the gallbladder will fill is by an increase in pressure in the common duct. When the gallbladder evacuates its contents, the pressure in the common duct falls.

This indicates that the flow into or out of the gallbladder is unidirectional at any time, and there is, therefore, no need for baffle plates to permit bidirectional flow at the same time.

It has been suggested that the free passage of fluid through the cystic duct does not occur unless sufficient pressure has been established to distend the duct system. Some have gone so far as to state that a sphincter is present between the body and neck of the gallbladder. It appears that in the intact gallbladder there may be an obstacle to the progress of fluids into or out of the gallbladder between the body and the cystic duct. While no definite sphincter has been demonstrated, one must admit the possibility that a sphincter may exist without an organized muscle band that can be demonstrated anatomically. The cardiac sphincter of the stomach is an illustration of such a possibility. In examining the gallbladder, however, one finds that the two locations where sphincters have been suggested are anatomical sites of bends in the continuity of the gallbladder. These bends in some instances represent a change in direction amounting to 180°.

The cystic duct is an anatomical pathway between the reservoir for bile on one side and the ducts connecting the liver to the duodenum on the other. It is subjected to varying pressures, from the gallbladder up to 25 cm. of bile pressure, and from the common duct up to 80 cm. of bile pressure. The gallbladder pressure is acquired directly from the tonic contraction of its musculature and possibly to some extent indirectly from the pressure of adjacent viscera or is transmitted from the thorax. In the common duct, the pressure is determined by the action of the sphincter of Oddi plus the tone of the duodenal musculature. The cystic duct is devoid of any organized system of musculature, which by itself could by contraction produce changes in the internal pressure in the cystic duct.

Thus, the cystic duct is a pathway through which bile is passing either into or out of the gallbladder. It is subjected to variations in pressure which take place normally on either end. These pressure changes may be a cause for sudden distention. The presence in the cystic duct of numerous nerve ganglia makes this a sensitive portion of the extra hepatic biliary passages. It is possible, therefore, that the existence of the "valves" of Heister is to retard the distention of the duct during the changes in pressure. Also, as suggested by Keith, they may maintain the patency of the lumen. In those instances where the distal portion of the cystic duct is devoid of valves (pars glabra), dilatation may be present (Fig. 4). This would indicate that the folds in the pars convoluta prevent dilatation of the cystic duct. The folds, or "valves," of Heister simply constitute an architectural device to maintain the uniform size of the duct in the presence of changing

pressures in the gallbladder or common duct, and to prevent sudden distention or collapse of the cystic duct. Thus, the presence of the "valves" of Heister, when normal, constitutes an anatomic factor of safety which seems to have been associated from the evolutionary viewpoint with the assumption of the erect posture.

APPLIED PHYSIOLOGY

The narrowness of the channel which connects the gallbladder to the common duct predisposes it to obstruction. Edema of the wall or of the mucosa alone, even though slight, may be sufficient to produce interference with the filling or the emptying of the gallbladder. The duration of this obstruction will, to a certain degree, determine the extent of permanent change, since inflammation with damage to the mucous membrane results in altered physiology of the gallbladder. While inflammation may occur in the gallbladder or the hepatic and common ducts, the narrow, tortuous channel in the cystic duct may be more readily occluded.

Anatomic relations of the cystic duct to adjacent organs predispose to pathologic changes. The venous plexus covering the cystic duct may involve the duct, especially when thrombophlebitis or thrombosis of the veins takes place. The cystic artery, too, may be involved in an inflammatory process and cause a change in the vascularity of this part. Angulation of the duct and the presence of swollen lymph glands adjacent to the cystic duct may also serve to produce obstruction.

SUMMARY

The "valves" of Heister arise late in the phylogeny of the mammalian kingdom. They are found only in primates. The human gallbladder is derived from a rapidly growing tube lying in a more slowly growing mesodermal bed. This difference in growth causes numerous foldings and windings to occur so that the gallbladder may be accommodated in its liver bed of limited space. The cystic artery early in development limits the longitudinal growth of the neck and cystic duct. Folds occur commonly in the fundus and body of the gallbladder and represent the most frequent anomaly of the human gallbladder. The "valves" of Heister are an embryological formation due to the winding or longitudinal compression of the duct during its development. The variations in the number and size of the "valves" and their absence in the more distal portion of the cystic duct are due to the variations in the size of the parts that take part in the foldings and winding. Our studies show that pressure variations on either side of the valvular portion of the cystic duct are not influenced by the presence of the "valves." Variations in pressure noted by Johnson

and Brown, and Lohner are probably due to the presence of the bends in the neck of the gallbladder. Inflammation of the "valves" may be responsible for obstruction of the cystic duct.

CONCLUSIONS

The function of the "valves" of Heister (if a function is to be ascribed to this anatomic formation) is to prevent distention or collapse of the cystic duct when sudden change of pressure occurs in the gallbladder or common duct. The folds, or "valves" of Heister, constitute an architectural device to maintain the uniform size of the duct in the presence of changing pressures in the gallbladder and common duct. Thus, the presence of the "valves" of Heister, when normal, constitutes an anatomical factor of safety which seems to have been associated from the evolutionary viewpoint with the assumption of the erect posture.

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NUTRITIONAL EDEMA: ITS EFFECT ON THE GASTRIC EMPTYING TIME BEFORE AND AFTER GASTRIC OPERATIONS

P. M. Mecray, M.D., Robert P. Barden, M.D., and I. S. Ravdin, M.D.,
Philadelphia, Pa.

(From the Harrison Department of Surgical Research and the Department of Roentgenology, School of Medicine, University of Pennsylvania)

ONE of the most common conditions with which surgeons are confronted is malnutrition. Its existence is far more widespread than is commonly believed, and its effects, while generally thought to bear some relationship to resistance, are actually of a more profound character. Prolonged restriction of protein in the diet causes a reduction of the plasma proteins. The chief function of the proteins in the blood is to maintain the colloid osmotic pressure of the circulating blood.[1] As Starling[2] has pointed out, the osmotic pressure of the plasma crystalloids, although relatively large (5,000 to 6,000 mm. of mercury) as compared with that of the plasma proteins (30 mm. of mercury), is of little importance in the normal fluid distribution, because crystalloids pass freely through the walls of blood vessels. Govaerts[3] and Schade and Claussen[4] found that as the plasma proteins were reduced from their normal of 7 per cent, the osmotic pressure exerted by the plasma was proportionately reduced. Weech and his coworkers[5] have shown that as the plasma proteins are reduced in concentration, the circulating fluid begins to leave the vessels, resulting first in a latent, and later in an evident edema. Their work indicates that the so-called critical level for edema (usually stated to be 5.2 gm. of protein per 100 c.c. of blood) is but the level at which edema becomes clinically manifest. This rôle of the plasma proteins, wherein they play an important part in maintaining a delicate state of balance between the blood and the intercellular fluid, is of particular importance to the surgeon. The observation that surgical patients may exhibit a definite hypoproteinemia, with or without edema, is becoming more generally accepted. Jones and Eaton[6] reported thirty-four cases which they had personally observed. We have observed six patients with hypoproteinemia in our surgical service in the past eight months. It is interesting to note that with the exception of the

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paper by Jones and Eaton in 1933 and the papers by Ravdin in 1935,[7, 8] the importance of nutritional edema affecting the gastrointestinal tract has not been stressed by writers on gastrointestinal surgery. We have on a number of occasions had evidence that a reduction of the plasma proteins may cause such changes in the gastrointestinal tract after gastrointestinal operations, that the postoperative picture mimics in every way a technical defect of the anastomosis. The following case history is illustrative:

Fig. 1.—Gastrointestinal roentgenogram twenty-four hours after administration of barium and nineteen days after operation.

CASE 1.—W. S., male, aged forty-two, was admitted to the Surgical Division of the Hospital of the University of Pennsylvania on September 18, 1933, with a diagnosis of duodenal ulcer. The roentgen studies had disclosed a marked pyloric obstruction. Restriction of food intake had resulted in a loss of forty-eight pounds. There was no evidence of peripheral edema; the patient, on the contrary, showed definite evidences of dehydration. On admission the hemoglobin was 102 per cent and the plasma proteins were 7.8 gm. per 100 c.c. of blood. A pylorectomy was performed with reconstruction of the gastrointestinal continuity by the Polya technic. Subsequent to operation the patient was given normal saline solution intravenously, and siphon drainage of the stomach was instituted. On the nineteenth day after operation,

there was no evidence that the stoma was functioning. At this time the serum proteins were 5.1 gm. per 100 c.c., and roentgen studies showed almost complete obstruction at the site of the stoma (Fig. 1). Peripheral edema was evident. We were successful at this time in passing a Levine tube through the patient's stoma, through which vigorous protein therapy was instituted. In addition to this the patient was given repeated blood transfusions. Within three days, there was marked clinical improvement, and roentgen studies on the twenty-ninth postoperative day disclosed a normally functioning stoma (Fig. 2).

It was exceedingly difficult to refrain from doing a secondary operation when roentgenographic evidence of obstruction was obtained, but a regime which tended to re-

Fig. 2.—Gastrointestinal roentgenogram thirty minutes after the administration of barium and twenty-nine days after operation.

store the plasma proteins resulted in their rapid rise and complete disappearance of the supposed technical defect in the anastomosis. We had observed a similar instance of this condition as early as 1928. In this patient, restriction of fluid intake and blood transfusions resulted in a functioning stoma. It occurred to us that not a few of the patients who were subjected to secondary operations after surgical procedures for gastric or duodenal ulcer, or malignancy, might in reality be examples of a profound disturbance of the plasma proteins with a state of edema affecting the site of the anastomosis. It seemed important to test the hypothesis that a relationship existed between gastric retention and the nutritional state.

METHOD

Dogs were chosen as the experimental animal for the following reasons: first, their size, which (a) facilitated plasmapheresis, (b) made it possible to take frequent blood samples, (c) made operative procedures satisfactory; second, the ease with which the dog could be adjusted to an unusual diet; third, the facility with which the animal could be trained to lie quietly before the fluoroscope. There were definite objections to the use of this animal. It normally has a low standard level of plasma proteins (mean about 5.8 per cent) and furthermore, different animals show a marked variation from the normal (5.0 per cent to 6.8 per cent). It resists the production of clinical edema, and it has a high susceptibility to distemper when malnourished.

The animals were carefully watched for changes in their physical state. The gastric emptying time and serum proteins were determined at least weekly. Total proteins only were determined. Weech, Reeves, and Goettsch[9] have demonstrated that the globulin fractions maintain a fairly constant level even when there is a marked decrease in the serum albumin. Thus, total protein values reflect changes in the more important albumin fraction. The Moore and Van Slyke[10] specific gravity method was used because of its simplicity, rapidity, and high degree of accuracy; which last compares favorably with Kjeldahl determinations. In determining the proteins, serum was used instead of plasma because of greater accuracy.[11]

A special 2 c.c. specific gravity bottle having a fine capillarity is required for the test. It should be rimmed with stopcock grease to prevent evaporation of its contents. It is carefully filled with serum, weighed accurately to within 0.1 mg., and corrected to 20° C. Per cent total serum proteins may be calculated from the following formula:

$$\text{Per cent total serum protein} = \left\{ \frac{\text{Weight of serum at 20° C.}}{\text{Weight of water at 20° C.}} - 1.007 \right\} \times 343$$

Care must be taken to keep all apparatus dry, preferably in a desiccator, to wipe away all excess serum or water before weighing, and to allow the samples to reach the temperature of the balance case before the final weighing. It is advisable to check all results by using two or more bottles. Variation between checks should not exceed 0.05 per cent.

Blood chloride determinations were made at critical stages in the experiments and were in every case within normal limits.

Hypoproteinemia was produced by diet and plasmapheresis. It was not found practical to plan in advance the number of plasmaphereses required in any particular animal, or the length of time the animal should be kept on a restricted diet. Numerous diets were tried early in

the experiments and the one found most satisfactory was a modification of several previously reported. The total stock diet was made up as follows:

Carrots	10 pounds	4.5 kilograms
Turnips	10 pounds	4.5 kilograms
Rice	4½ pounds	2.0 kilograms
Oleomargarine	3½ pounds	1.6 kilograms
Karo	3½ pounds	1.6 kilograms
Cod liver oil	100 cubic centimeters	
Bone ash	50 grams	
Sodium chloride	100 grams	
Yeast concentrate	5 grams	

The carrots and turnips were coarsely ground and were boiled for twenty minutes along with the rice. The other ingredients were then added, with the exception of the cod liver oil and yeast, which were not added until the mixture had cooled. The stock food was carefully mixed and kept in a refrigerator room. The dogs were given daily all they desired, care being taken that each animal received at least double its basal caloric requirement. The protein content was approximately 1 per cent.

It was found that the injection of a normal saline solution into the saphenous vein to equalize the amount of blood withdrawn from the femoral artery facilitated the plasmapheresis. By this means as much as 950 c.c. has been withdrawn from a dog weighing 9 kg. without producing any distressing symptoms. It is obvious that the protein content of the mixture of blood and saline is not as high as that of whole blood, but the lack of evident shock enables the worker to take the time to wash the corpuscles before replacing them intravenously.

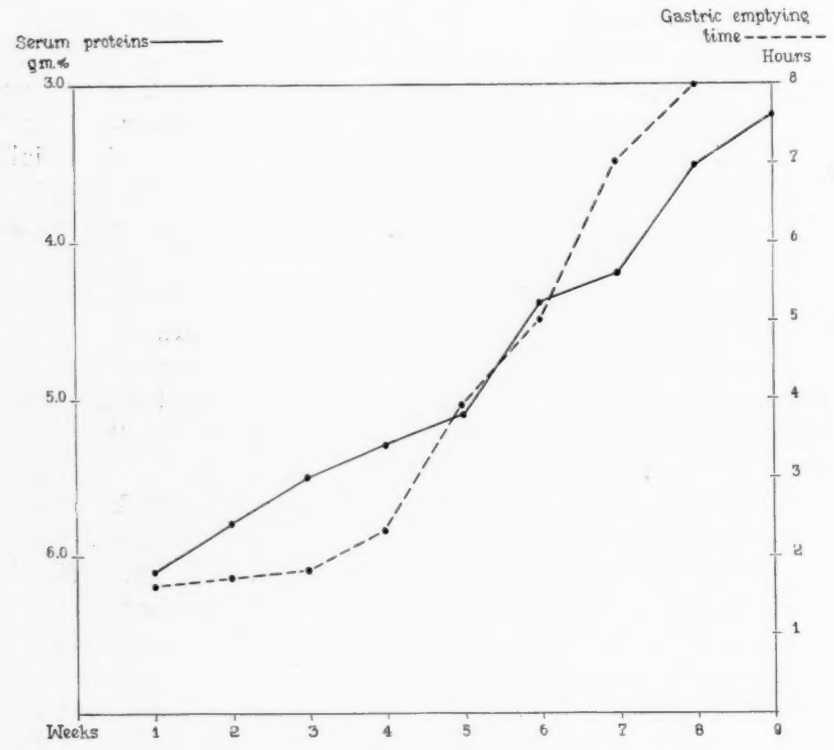
Three groups of experiments were carried out. First, the effect of hypoproteinemia on the gastric emptying time was determined on unoperated dogs. In the second group, animals were made hypoproteinemic and then were subjected to pyloric resection with restoration of the gastrointestinal continuity by gastroduodenostomy or by the Billroth II principle. The gastric emptying time was determined at critical periods of the experiment. After a period of hypoproteinemia, the proteins were permitted to rise and at a subsequent period were again reduced. In group three, dogs which had Polya operations performed on them at least a year previously were studied. These animals were checked weekly as the proteins were lowered, raised, and then lowered. Needless to say, not all the animals survived the rigors of the course outlined for them.

RESULTS

Group I was composed of ten dogs, eight of which survived the low protein diet and repeated plasmapheresis for more than one month. Of the eight animals, two showed little change in their gastric empty-

ing time as the serum proteins were reduced. One of these had a nearly normal emptying time despite a serum protein of 2.73 per cent. At postmortem twenty-four hours later, there was obvious edema of the gastrointestinal tract.

The remaining six animals showed varying degrees of retention of the barium meal as the serum proteins were lowered. In one dog the gastric emptying time after reduction of the serum proteins was fifty times the normal for this animal, while in another it was thirty times the normal. In general in this group the lower the serum proteins, the longer was the gastric emptying time (Fig. 3).



Dogs 44 46 47 149 150 299 351 352 — Group I.

Fig. 3.—Group I. Mean values for serum proteins and gastric emptying time.

Group II was composed of three dogs which when hypoproteinemic were subjected to pylorectomy. In two of the three animals in this group the serum proteins were reduced a second time after recovery from the initial low values. In the first period of low protein diet, none of the animals had total serum protein values below 4.0 per cent. This may be roughly compared to a serum protein of 5.5 per cent in the human being. In our experience it was the lowest value we were able to obtain and keep the animals well enough to regain a normal serum protein after the addition of sufficient protein to the diet.

After operation, while the serum proteins were low, there occurred a definite delay in the gastric emptying, despite strong gastric contractions on fluoroscopic examination (Fig. 4). All of the animals showed speeding of the gastric emptying as the proteins were restored to normal (Fig. 5). The two animals having their serum proteins reduced a second time showed slowing of their emptying times as hypoproteinemia was again induced.

Fig. 4.—Fluoroscopic examination in a dog with low serum proteins.

In one of the dogs all fluids were withheld for several days. The gastric emptying time was speeded up. Following this, 800 c.c. of normal saline solution were given intravenously. The serum proteins fell and the gastric emptying was retarded (Fig. 6).

Group III consisted of two animals which had been subjected to the Polya operation over a year before the beginning of this experiment. Their gastric emptying time was studied repeatedly while they were

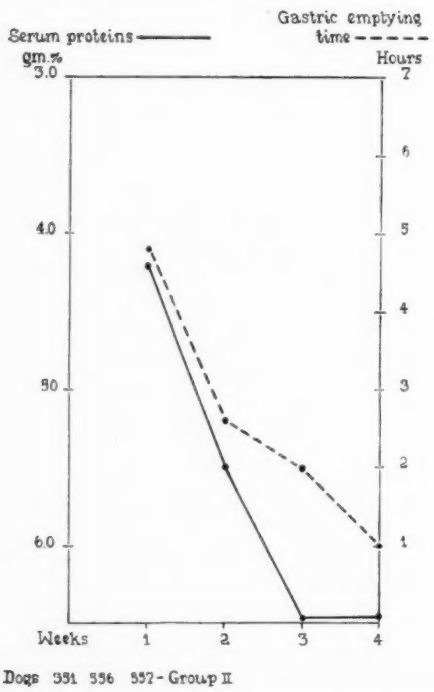


Fig. 5.—Group II. Mean values for serum proteins and gastric emptying time.

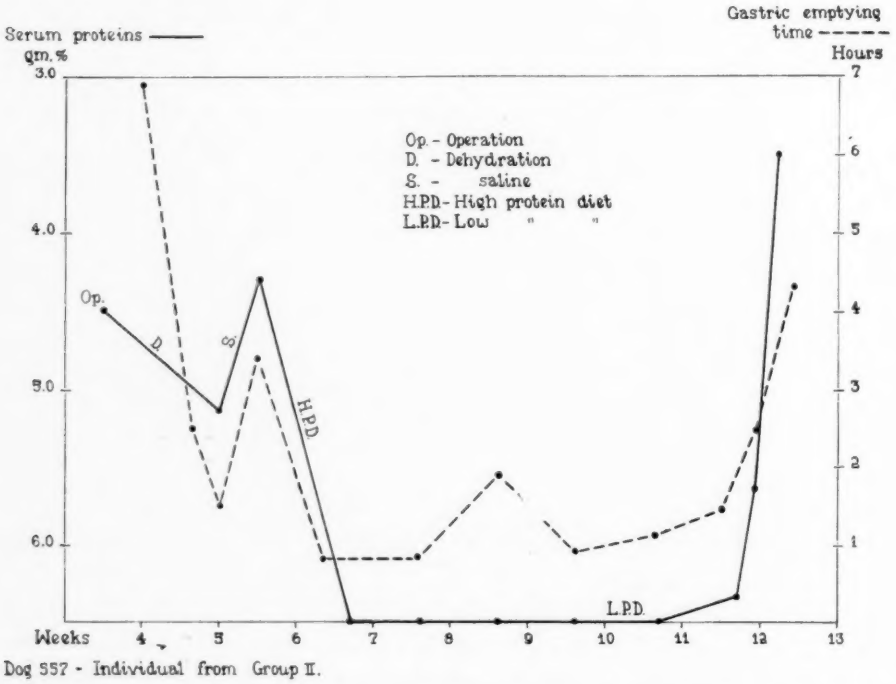


Fig. 6.—Effect of high and low serum protein on the gastric emptying time in dog No. 557.

on a normal animal house diet and after varying periods of a low protein diet and repeated plasmapheresis (Fig. 7).

The dogs showed a marked retardation of the gastric emptying time as the serum proteins fell. In Dog No. 687, as the serum proteins were restored to normal, the gastric emptying time was speeded up to that observed during the control period. When the serum proteins were reduced a second time, the gastric emptying time as observed fluoroscopically was not retarded as it was on the first period of hypoproteinemia, although there was definite clinical evidence of gastric retention. This was manifested by the retention of gastric contents as evidenced by the daily passage of a stomach tube.

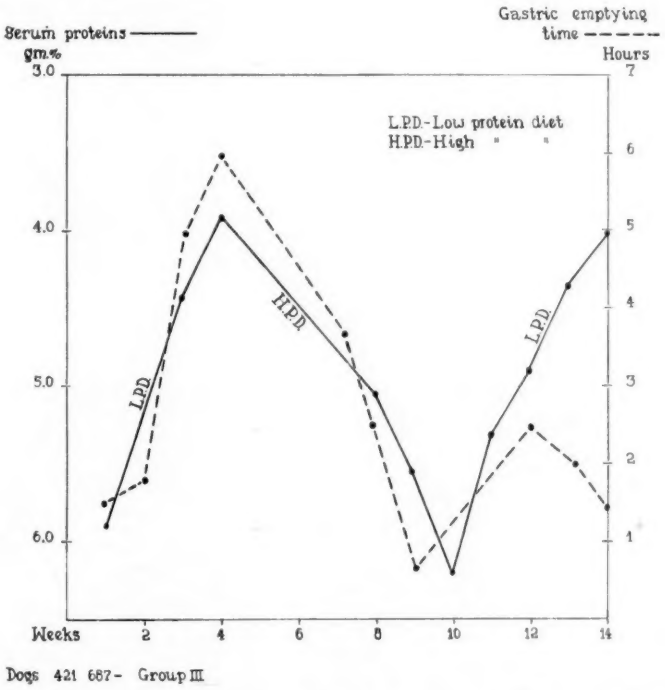


Fig. 7.—Group III. Mean values for serum proteins and gastric emptying time.

DISCUSSION

There are several possible explanations for the observed delay in gastric emptying time in hypoproteinemic patients and animals. First, the reduced vitality observed in the hypoproteinemic dogs may have an expression in a diminution of gastric activity. Second, the edema of the gastric tissues may interfere with effective muscle contraction. Third, the reduction in the size of the stoma coincident with the edema may so interfere with emptying as to result in the observed retention.

We are inclined to believe that this latter explanation is the correct one. All of the animals with total serum proteins of 4.0 per cent or lower showed gross edema of the stomach at postmortem or operation.

The same state has been observed in human patients with hypoproteinemia. When operation has been resorted to, the increased edema incident to trauma further reduces the caliber of the stoma.

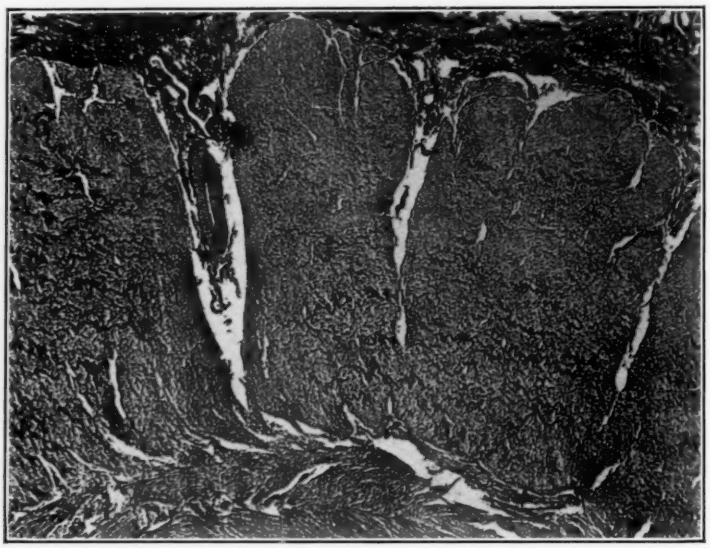


Fig. 8.—Photomicrograph showing submucosa and muscularis of the stomach of a normal dog. Total serum proteins 6.20 gm. per cent. (×50.)

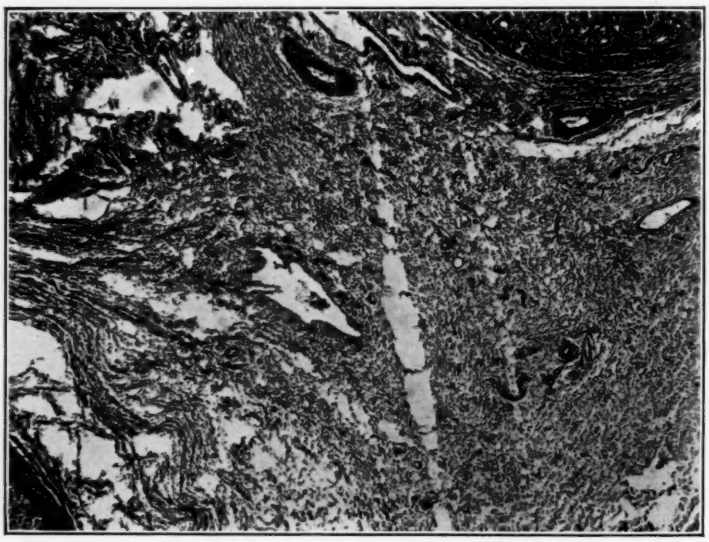


Fig. 9.—Photomicrograph showing edema of the submucosa section from animal having total serum proteins of 2.73 gm. per cent. (×50.)

Sections of the specimens removed from the stomach demonstrate the edema (Figs. 8 and 9). We have examined the stoma at postmortem in five hypoproteinemic dogs subjected to the Polya operation and in which the period following operation was sufficiently long to

permit subsidence of the reaction to the trauma of operation. In four of the five instances, the edema was such as to cause a very marked reduction in the size of the stoma.

It was a general observation, during fluoroscopic examination of the animals having edema, that the gastric tone was normal or increased, and that the peristaltic waves were equal to, or greater than, their normal depth, although motility was practically absent. The fluoroscopic picture was similar to that observed during pyloric obstruction.

During this investigation, several observations of a general nature have been made. In our experience animals rendered definitely hypoproteinemic all developed ulcers over their forelegs and ankles. These ulcers increased in size as the proteins were further reduced and healed rapidly as the proteins were raised. Marked difficulty was noted in healing of the abdominal incisions of hypoproteinemic animals. When the proteins were raised, the wounds healed promptly. It was interesting to note that we have seen two instances of intestinal perforation in hypoproteinemic animals. One was a perforation of an ulcer in the proximal duodenal stump five weeks after operation, and the other was a perforated gastrojejunal ulcer fifteen months after the operation.

Despite the fact that the dogs maintained on the low protein diet consumed more than double their basal caloric requirements, they invariably lost weight which amounted in several instances to as much as 40 per cent of their original body weight. Although the proteins were raised from a level of 4.0 per cent to a normal figure in approximately three to four weeks on the high protein diet alone, the gain in weight proceeded at approximately half that speed, and in no instance, even after two months, was the original weight regained. Animals in the hypoproteinemic state were, in our experience, extremely susceptible to distemper. None of our dogs received prophylactic injections.

Numerous opportunities were afforded to study the dilution of blood plasma caused by intravenous injections. On seven occasions an average of 375 c.c. of normal saline caused the proteins four hours after the infusion to be reduced from a mean of 4.6 to a mean of 3.7 per cent.

Clinically, latent or manifest edema is most frequently seen in cases of nitrogen starvation, general malnutrition, purulent and serous drainage, hemorrhage, severe diarrhea, and following the administration of large amounts of sodium salts. It has been indicated by Weech and Ling,[12] by Lepore,[13] and others that, if the sodium ion is restricted, it is difficult to produce edema in either dogs or human beings regardless of the plasma protein level. There is good evidence that as the plasma proteins are reduced from their normal levels, diminishing amounts of fluid and sodium salts are required to cause edema. It must

be remembered that the evident edema of the subcutaneous tissues is but an external manifestation of a general process and as such requires active therapy if the patient is to survive.

Therapeutic procedures include transfusion, salt restriction, administration of acacia and a high protein diet. Liu, Chu, Wang, and Chung[14] had a remarkable opportunity to test the powers of various foodstuffs in regeneration of the plasma proteins. They concluded that 1 gm. of animal protein was equivalent to 2 gm. of vegetable protein. Soy beans seem to be the exception to this. Indeed, McNaught and his coworkers[15] maintain that it is the best food for rapid regeneration of the proteins.

As prophylaxis against edema formation Jones and Eaton,[6] in their excellent clinical paper, warn against too free an administration of alkali in ulcer patients. They recommend also that not over 3,000 c.c. of normal saline solution be given daily. They suggest determinations of blood plasma proteins in all patients in whom there is a possibility of hypoproteinemia. It must be stressed, however, that a dehydrated patient may show normal or even high plasma proteins. Yet once the dehydration is overcome, the patient may be found to be hypoproteinemic and may be edematous.

SUMMARY

We have presented data on the effect of a reduction of the serum proteins on the gastric emptying time. In general, the gastric emptying time increases as the serum proteins decrease in concentration. This is true whether the stomach is intact, or whether it has been subjected to a short-circuiting operation. The prolongation in gastric emptying time is associated with edema of the gastric wall. The implications of these findings to the surgeon are pointed out.

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INTESTINAL OBSTRUCTION COMPLICATING PREGNANCY

ELDRIDGE L. ELIASON, M.D., AND WILLIAM H. ERB, M.D.,
PHILADELPHIA, PA.

THE possibility of pregnancy per se causing intestinal obstruction will probably be questioned by a great many obstetricians and surgeons. In none of the standard textbooks on obstetrics or surgery is there any reference to pregnancy itself being an etiologic factor in ileus. Leonard[1] in 1917 writes that "normal intrauterine pregnancy rarely if ever causes acute obstruction per se." A French author, Pinard, states, "I have never seen intestinal occlusion complicate a normal pregnancy." Wilms, in his monograph, *Der Ileus,* makes the statement that ileus caused by pregnancy alone belongs to the rarest of conditions. With this point of view prevailing, it was thought worth while to present three cases in which the most likely cause of the ileus was the normal intrauterine pregnancy. Briefly, the other causes of intestinal obstruction complicating pregnancy are also discussed.

The broader field of obstruction complicating pregnancy has received very little attention from English authors. The German literature, however, is relatively rich with contributions on the subject. Ludwig[2] in 1913 was able to gather 95 cases from the literature. The etiology and mortality in these cases are shown in Table I. Von Mikulicz-Radecki[3]

TABLE I

COLLECTED CASES TO 1913 (LUDWIG)

ETIOLOGY	NO. OF CASES	DEATHS	UNKNOWN	MORTALITY
Adhesions	28	17	2	65%
Volvulus	13	9	1	75%
Invagination	4	3		75%
Pregnancy	10	4	1	44%
Hernia	7	3		43%
Miscellaneous (Including tumors, cysts, exudates, etc.)	33	13		39%
Total	95	49	4	54%

collected all the reports from 1913 to 1926 and found 74 cases, to which he added 7 more from his own clinic. These are summarized in Table II.

TABLE II

COLLECTED CASES 1913-1925 (MIKULICZ-RADECKI)

ETIOLOGY	NO. OF CASES	DEATHS	UNKNOWN	MORTALITY
Adhesions	15	6		40%
Volvulus	34	14	4	47%
Invagination	3	3		100%
Tumor	4	2		50%
Pregnancy certain	10	2		20%
Pregnancy uncertain	8			
Unknown	6		6	
Total	80	27	10	39%

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Since then, 63 cases have been reported, to which the authors have added 3 from their own experience. Table III shows an analysis of these.

TABLE III

COLLECTED CASES 1925-1935 (ELIASON AND ERB)

ETIOLOGY	NO. OF CASES	DEATHS	MORTALITY
Adhesions	14	3	21%
Volvulus	11	4	36%
Tumors and cysts	7	2	29%
Paralytic (inflammatory)	4	2	50%
Hernia	2	-	----
Pregnancy	28	3	11%
Total	66	14	21%

A review of these figures emphasizes at once the great frequency with which adhesions and volvulus appear as the cause of the obstruction and the infrequency with which strangulated hernia appears.

The cause for this can be explained very logically. The great distortion caused by the growing uterus would naturally change the normal relationships of the abdominal viscera. Adhesions, therefore, which had previously been of no significance, now cause kinking of the bowel and eventually obstruction. This assumption is further confirmed by the

TABLE IV

ILEUS IN RELATION TO MONTH OF PREGNANCY

MONTH	LUDWIG	MIKULICZ-RADECKI	ELIASON AND ERB	TOTAL
1	0	0	0	0
2	1	2	1	4
3	5	1	0	6
4	9	3	6	18
5	9	7	13	29
6	7	12	8	27
7	8	9	6	23
8	8	5	11	24
9th and birth	20	17	19	56
Puerperium	14	11	2	27

incidence of obstruction in relation to the month of pregnancy (Table IV). Both Ludwig[2] and Mikulicz-Radecki[3] found that there were three periods during gestation and puerperium when obstruction was more likely to occur: (1) during the fourth and fifth months of pregnancy when the enlarging uterus no longer remains a purely pelvic organ, (2) during the eighth and ninth months when the fetal head again descends into the pelvis, and (3) during delivery and the early days of the puerperium when there is a marked change in the size of the uterus. These three periods represent the times when there is likely to be the most disturbance of the normal intraabdominal relationships.

Strangulated hernia rarely appears as a cause of intestinal obstruction. Ludwig[2] and Mikulicz-Radecki attribute the displacement of the intestines by the growing uterus, away from the inguinal and femoral rings, as the reason for this relative infrequency. Most of the cases reported are due to umbilical and incisional hernias where this factor of

small gut displacement would not come into play. One of the two cases recorded in Table III was due to an epigastric hernia and the other to an umbilical one.

In comparing Tables I, II, and III one notices the greater frequency with which pregnancy per se appears as an etiologic factor in cases reported from 1926 to 1936. This is probably not a true state of affairs, but due to the great interest shown in this subject by the German authors. It is very likely that many cases of obstruction due to the usual etiologic factors, such as adhesions, tumors, volvulus, etc., have not been considered of sufficient interest to report in later years. Therefore, the relative incidence of 10 cases due to pregnancy itself out of 95 cases (Ludwig's[2] statistics) is a more accurate incidence than 28 cases out of 66 (Eliason and Erb).

These cases of true "pregnancy ileus" have nearly all been proved by excluding other causes either by laparotomy or autopsy. Only a few of them have been accepted as true cases on the clinical course or on the basis of complete relief following emptying of the uterus. The site of obstruction in all the cases has been low in the sigmoid, approximately where the sigmoid crosses the innominate line.

Why pressure from the pregnant uterus should cause obstruction in a very small percentage of pregnancies and not in others, where the same factors appear to be present, is an enigma. Many interesting facts and theories have been advanced to explain this phenomenon. One interlying factor common to all cases is that in pregnancy the female is even more constipated than usual. If, to this manifest lack of tone, other elements are added, one can conceive that the pressure of the pregnant uterus completes the picture. In other words, the pressure of the pregnant uterus itself would be unable to produce obstruction in a normal person. Two of these extraneous factors are clearly illustrated in Cases 1 and 2. In Case 1 the patient had a megacolon, while in Case 3 the paresis following a laparotomy may have so interfered with intestinal motility that the pressure of the pregnant uterus was sufficient to result in complete obstruction. Mechanical factors, such as[2] retroflexed uterus,[17] hydrocephalus,[27] hydramnios, and a congenital adhesion in a case of Leonard's[1] which bound the sigmoid to the lateral pelvic wall and prevented its displacement, are also factors which come into play.

The theory of atonia or disturbance of the vegetative nervous system has its strongest supporters in Stoeckel[4] and his school. It is discussed especially in relation to the 9 cases in the literature,[3, 22, 25, 29, 36, 43, 44] in which in addition to an ileus a preexisting severe pyelitis was present. In these cases there was marked stasis and dilatation of ureters, as shown by urograms. Whether this retroperitoneal inflammation was a predisposing cause to a partial paralytic ileus or whether this atony of the ureters is part of some pathologic disturbance is open to conjecture. Some authors even suggested that the intestinal stasis came first, with

flooding of the system with colon bacillus resulting in pyelitis (in 8 out of 9 cases the organisms recovered from the urine were colon bacilli). The probability that this atonia is due to some disturbance of innervation is further strengthened by the fact that in two cases[29, 32] in which a cesarean section was done to relieve the obstruction due to the pregnancy, a subsequent hysterectomy had to be performed because of hemorrhage resulting from failure of the uterine muscle to contract.

The mortality figures in Tables I, II, and III demonstrate that therapy in reported cases has not been very successful. Case histories show that probably the most important factor in maintaining this high mortality rate has been delay in adequate treatment. Mikulicz-Radecki[3] attributes the drop in his statistics to 39 per cent from 54 per cent in Ludwig's[2] to more prompt consultation with a surgeon. This mortality rate has still further been improved, so that at present it is 21 per cent. If one is alarmed at the high maternal death rate, there is still further cause for alarm in the higher fetal death rate, which the earlier authors said varied between 66.6 per cent and 75 per cent. Unfortunately, the same degree of improvement is not shown in later years as in the maternal mortality rate, so that in 62 cases in our series in which the outcome as to child is mentioned only 31 or 50 per cent of the children survived.

Delay in treatment is much more likely to occur in ileus accompanied by pregnancy than in ileus in a nonpregnant person. Many of the cardinal symptoms of obstruction, with no pathologic significance, are found during a normal gestation. Constipation is the rule in the female, and this is more true during pregnancy. Furthermore, the nausea and vomiting of early pregnancy is also a confusing factor in the first four months, but fortunately very few cases of obstruction occur at this time. A differentiating feature between nausea and vomiting of early pregnancy and that of obstruction is the fact that the abdomen is sunken and not distended in the former. Later, during labor, one might readily mistake the crampy, colicky pain of an intestinal obstruction for normal labor pains. There are many reasons for the delay, though these reasons should not excuse it, because if the possibility of obstruction is considered, the differential diagnosis can be made.

Once the diagnosis of obstruction in pregnancy has been made, it must be decided most promptly whether the obstruction is due to pregnancy itself or to some other factor. The following facts should be borne in mind in making the differentiation. Obstruction due to pregnancy is low in the intestinal tract and is simply an occlusion. The symptoms, therefore, develop slowly and often when first seen the patient simply complains of failure to have had an adequate evacuation for four or five days. Distention quite frequently dominates the picture. This state of affairs is in contrast to volvulus or strangulation due to adhesions, when severe agonizing constant pain accompanied by shock is the outstanding finding. The x-ray, which is invaluable in helping to make the differentiation, shows gas in the large intestine and later also

in the small intestine. The site of obstruction is shown by the barium enema to be located at the rectosigmoid junction when due directly to pregnancy. Great care must be exercised in diagnosing obstruction due to pregnancy in patients with previous laparotomies, because of the likelihood of adhesions.

Every one is agreed that immediate laparotomy following adequate preoperative preparation is the treatment of choice in those cases in which the pregnancy is not the etiologic cause. Several different plans of treatment, however, have been advanced in cases in which no other cause for the obstruction is found. In discussion of this phase of the problem, it was thought worth while to present the following three cases in detail:

CASE 1.—C. S., aged thirty-five years, had an appendectomy in 1927. Date of last period was Sept. 20, 1933. In the third month of her pregnancy she had lower abdominal cramps with bloody discharge, which was diagnosed as threatened abortion. She recovered completely, however, and was perfectly well until three days before admission. Admitted to the Obstetrical Service of Dr. Charles C. Norris, March 3, 1934, at 8:30 P.M. with history of three days' constipation and generalized lower abdominal pain. On the morning of admission she had taken an aperient with no result. Temperature was 99° F., pulse 80, and respirations 24. Abdomen was distended and peristalsis moderately active. No tenderness or rigidity present. The uterus was the size of a five months' pregnancy. Six hours later, enemas were repeatedly unsuccessful and distention had increased. The patient was becoming stuporous. Fluids were given by hypodermoclysis and intravenously. Wangensteen suction was started. An x-ray of the abdomen in the morning after admission revealed gaseous distention of the colon with no gas in the small intestines. Barium enema showed a complete obstruction at the junction of the sigmoid and rectum. Patient was transferred to the surgical service. Findings on admission to surgical service were: temperature 100.2° F., pulse 98, respiration 19, blood pressure, 134/76. Patient intermittently rolled about the bed moaning and groaning with pain. Abdomen was markedly distended, literally "tight as a drum." Peristalsis was infrequent, and when heard at all it was definitely tinkling and hollow in character. Percussion was not tympanitic. It was thought unwise to attempt more than a cecostomy. This was done according to the Witzel technic on March 4, 1934. Following this, the patient improved somewhat, though considerable difficulty was still experienced in combating the distention in the large bowel. Because of this, it was decided to sacrifice the child in order to facilitate further surgery, for at this time the diagnosis was carcinoma of the rectosigmoid. After failure of medical induction, a surgical induction of labor (introduction of a Voorhees bag) was attempted on March 13. Patient was finally delivered of a twenty-five-week-old fetus on March 15. On March 20, she had a normal bowel movement. Barium enema on March 27 was negative. Sigmoidoscopic examination on April 2 was negative. The cecostomy tube was now clamped for three days and then removed. Convalescence was uneventful. On September 17, 1935, one and a half years later, a barium enema revealed a megacolon holding 4,000 c.c. of barium with ease. She has remained perfectly well except for chronic constipation.

Discussion.—At the time of the first x-ray report of obstruction at the rectosigmoid junction, the pregnancy itself as an etiologic factor did not enter into the differential diagnosis. It was then the belief of the x-ray department, as well as of the surgical staff, that pregnancy per se did not cause obstruction. It was thought that the most likely cause

for the obstruction was an annular neoplasm of the rectosigmoid junction. Because of the marked distention and the poor condition of the patient, it was deemed homicidal to attempt to attack the point of obstruction, and therefore a cecostomy was done with the hope of preparing the patient for a resection of the malignant growth at a later date. Following the cecostomy, the discussion arose as to which of the following three was the proper procedure: (1) to allow pregnancy to go to term and after delivery to attempt radical surgery, (2) to do a laparotomy as soon as condition warranted and ignore the pregnancy, (3) to do a therapeutic abortion followed by laparotomy. The cecostomy did not function sufficiently well to warrant the first procedure. In addition, there was fear of metastasis (as carcinoma was thought to be the cause of obstruction) while we waited four months for the normal end of gestation. The size of the uterus would have made the second plan exceedingly difficult technically. Besides increasing the risk to the mother, it was felt that probably the fetus would be lost by abortion as a result of the surgical intervention. Therefore it was decided to follow the third plan of attack as outlined above.

The question might be asked as to how this diagnosis could have been made earlier and thus the life of the fetus saved. The knowledge that pregnancy sometimes causes obstruction would certainly have aided. Dr. Pendergrass, the roentgenologist, then suggested that if another such case would arise, it might be worth while to attempt an enema in the knee-chest position, in this way releasing the obstructed bowel from the pressure of the pregnant uterus. Keeping this in mind, it was our good fortune to be presented with a somewhat similar case nine months later and still another a year after that.

CASE 2.—E. L., aged twenty-two, primipara, gave a history of previous appendectomy. Catamenia were normal. Last period occurred July 20, 1934. There was slight nausea and vomiting in the afternoon during the early months of pregnancy, but this had ceased two weeks before admission. At 7 A.M., November 2, 1934, the day before admission, the patient got out of bed and became nauseated and vomited. This was accompanied by intermittent griping pains in the epigastrium. Upon return to bed she felt relieved. She repeated this several times during the morning. Six hours after onset, following an attempt to eat milk toast, her symptoms became more severe in spite of maintaining the supine position. Singultus began. The pain increased in severity. Vomitus changed from pure gastric contents and became tinged with green. Her family physician was promptly called. He advised an enema and gave her a hypodermic. This relieved the pain considerably. Enema was returned with small amount of feces. Pain and vomiting returned and enema was repeated. Again, this was only slightly effectual. Another enema was given which also did not relieve the patient. Because of the persistence of nausea, vomiting, and intermittent pain, she was referred to the hospital, eighteen hours after onset, with a tentative diagnosis of intestinal obstruction. Findings on admission: a young female, apparently acutely ill with abdominal pain, temperature 99° F., pulse 124, respiration 32, blood pressure 120/68, white blood cells 11,700. The lips were dry, and the patient was apparently dehydrated. Otherwise, the findings were negative except for those of the abdomen, which was distended, revealing also visible peristalsis. There was some tenderness in the epigastrium.

Peristalsis was hyperactive. Uterus was about the size of a four months' pregnancy. After a diagnosis of intestinal obstruction was made, she was given an x-ray examination to confirm the opinion and determine the point of obstruction if possible. By x-ray there was thought to be an obstacle at the region of the junction of the rectum and sigmoid. By changing the position of the patient on the table, barium passed into the remainder of the colon. The rectum and sigmoid appeared to be displaced as though they were riding over a mass. Following the suggestion of Dr. Pendergrass, the patient was given a soapsuds enema while in the knee-chest position. This was very effectual for feces and flatus and, in addition, relieved her of all her symptoms. She was kept under observation for two days and then discharged. She was delivered at term of a full-term living child. Colon by barium enema eight months later was reported as negative for any lesion.

CASE 3.—D. C., from the service of Dr. J. Vernon Ellson, Delaware County Hospital, white primipara, aged twenty-six years. Last period was on Oct. 20, 1935. During early pregnancy she was confined to bed with nausea and vomiting which, however, subsided in December. She was admitted to the hospital on April 3, 1936, with pain in her right lower abdomen. She had been nauseated and vomited four times the day of admission. In addition to this her bowels had not moved. The only other symptom of interest was burning on urination. Physical examination showed an adult female, not acutely ill, apparently six months pregnant, uterus at umbilicus, temperature 99°, pulse 82, respiration 20, blood pressure 110/64. The finding of tenderness over McBurney's point and spasm of the right lower rectus plus a leucocyte count of 13,800 with 77 per cent neutrophiles suggested a diagnosis of acute appendicitis, which was confirmed at operation. Her nausea and vomiting did not subside, however, and abdominal distention appeared. Vomiting increased in severity. An enema returned colored water, but did not relieve patient's symptoms. An x-ray examination on April 9, six days after appendectomy, was reported as follows: "A scout film shows marked distention of the large intestine and moderate distention of the small intestine. These organs are displaced in the usual manner due to a large gravid uterus, which is deflected somewhat toward the left side. The air in the colon diminishes and ends just above the brim of the pelvis. Barium enema easily filled the rectum and sigmoid to the level of the pelvic brim. There was slight delay at this point, then the barium passed beyond into the distended descending colon. With the patient lying on her back there is a pressure defect on the sigmoid at the pelvic brim. There is no evidence of any organic lesion at this point."

The patient was too ill and too distended to be placed in the knee-chest position. Therefore an enema was given with the patient lying on her right side and abdomen, and the foot of the bed elevated about eighteen inches. This resulted in expulsion of gas and barium. Distention subsided and vomiting became much less pronounced, and it also stopped shortly. The patient was discharged from the hospital April 17, with pregnancy uninterrupted. Progress of pregnancy uneventful to date, June 7, 1936.

Discussion.—Cases 2 and 3 illustrate the value of change of position to relieve pressure of the pregnant uterus on the sigmoid. This plan of therapy was thought to be original with the writers until it was found that Fleischhauer[5] mentions two successful cases and gives credit to Texiere as being the first to have suggested the idea. Halter[22] and Graff[21] also advise the knee-elbow position, but fail to mention any results obtained. Kemkes[28] reports an unsuccessful case; however, at laparotomy a ruptured uterus was found, with abdominal child occluding the colon at the hepatic flexure. Another interesting case which would

tend to support this plan of treatment is that of Hornung.[6] This patient developed obstruction during labor and intervention was postponed with the hope that the ileus would be relieved with the emptying of the uterus. After observing the patient for three hours after delivery and failing to note satisfactory improvement, a laparotomy was decided upon. At operation, distention of both large and small bowel was found. The distended large loop having been traced into the pelvis, the uterus had to be lifted. There was prompt evacuation of both flatus and feces on the table, with collapse of the distended bowel. Following the laparotomy, she made an uneventful convalescence. Steinitz[46] reports a similar case in which the obstruction corrected itself during preparation of the patient for a cesarean section. One might assume that these two cases could have been successfully treated by the knee-chest position.

The question, whether to terminate the pregnancy by the vaginal route or do a laparotomy, arose in past discussions. This should no longer be a point of debate. If the obstruction is not relieved by a high enema with change of position, a laparotomy is clearly indicated. If after the laparotomy, the obstruction is found to be due to the pregnancy itself, and the child is viable, the indication for a cesarean section is a clear one. If the child is not viable, it still would seem to be the safer course to empty the uterus, though possibly one might be able to correct the point of pressure by manipulation with the hand in the peritoneal cavity. Furthermore, if one had proved that there was no other cause for obstruction, it would be perfectly safe to empty the uterus by the vaginal route if symptoms did not subside following laparotomy. At operation, Sennewald[43, 44] suggests the insertion of a long rectal tube past the point of obstruction, with the aid of intraabdominal manipulation. This procedure seems to be of special value in cases in which the child is not viable and one hesitates to empty the uterus.

Any form of treatment except immediate laparotomy meets the criticism of the danger of delay, especially if the obstruction later proves to be due to volvulus or adhesions. This danger can be minimized if one bears in mind the previously mentioned differential points in symptomatology and the great value of the x-ray. Furthermore, preparation for laparotomy should be made while conservative measures are being tried, or as Dietrich[7] stated, "mit dem Messer in der Hand." The old axiom that an effectual enema is one that relieves the patient of his symptoms rather than one effectual for gas or feces will further protect the surgeon from needless delay.

SUMMARY

A review of the literature on intestinal obstruction complicating pregnancy emphasizes (1) the difficulty of diagnosis, (2) the high maternal and still higher fetal mortality, and (3) that though pregnancy

itself is a rare cause for the obstruction, it is not as infrequent as one might suspect from consulting standard textbooks on surgery and obstetrics.

Three additional cases are reported in which probably the pregnancy per se was the etiologic factor.

A conservative method of treatment (change of position) has been advanced and precautions discussed which should be followed.

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POTASSIUM IN ACUTE INTESTINAL OBSTRUCTION

JOHN SCUDDER, M.D., RAYMUND L. ZWEMER, PH.D., AND
RICHARD TRUSZKOWSKI, M.Sc., PH.D., M.D., NEW YORK, N. Y.

(From the Departments of Anatomy, Surgical Pathology and Surgery of Columbia University, College of Physicians and Surgeons, and of the Presbyterian Hospital)

ACUTE intestinal obstruction and adrenal insufficiency have many features in common.[1] In each, the cause of death has been variously ascribed to dehydration, electrolyte loss, or to an unknown toxin.

A series of researches by Zwemer and Truszkowski[2-5] have demonstrated that "the various known symptoms of corticoadrenal insufficiency may be explained in terms of a disturbance of corticoadrenal-potassium interrelations." In particular, the hyperpotassemia of certain phases of adrenal insufficiency was found to be of the same order as that associated with toxic symptoms in animals subjected to experimental chronic potassium poisoning.

It was therefore felt that the variations in blood potassium following acute intestinal obstruction should be investigated.

EXPERIMENTAL MATERIAL AND METHODS

Eight cats were used in the experiments; in 4 the intestines were obstructed with jejunal loops of various lengths and the remainder had simple obstructions at different levels of the alimentary tract (Table I). Aseptic technic, ether anesthesia, a midabdominal incision, and a minimum amount of handling of the viscera, allowed the animals to recover, with no sign of shock, within an hour of the operation. Cotton tape was used in making the obstruction and silk for closure. There were no complicating wound infections.

Blood potassium was determined by Truszkowski and Zwemer's[3] method for 0.2 ml. of cat whole blood. Whole blood determinations are permissible in the cat, since the potassium content of cells and plasma is similar and rise and fall together. Blood density was determined by the falling drop method of Barbour and Hamilton.[6, 7] The values given on the charts and in the protocols represent the means of two or more determinations.

EXPERIMENTAL OBSERVATIONS AND DATA

Group 1.—For the first group of four animals the procedure consisted of obstruction and interference with the vascular supply.

A. A closed 15 cm. jejunal loop was formed in Cat 3630 by tying one tape just below the ligament of Treitz and a second tape 15 cm. lower. The veins were

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ligated, and the mesentery was cut so as to eliminate the possibility of a collateral venous return, the arterial supply being left intact. The blood potassium and blood density were followed at two-hour intervals. The cat died 15 hours after operation, in a convulsion. *Autopsy:* Black intact loop bathed by reddish peritoneal fluid; the potassium content of the loop was 77.2 mg. per cent.

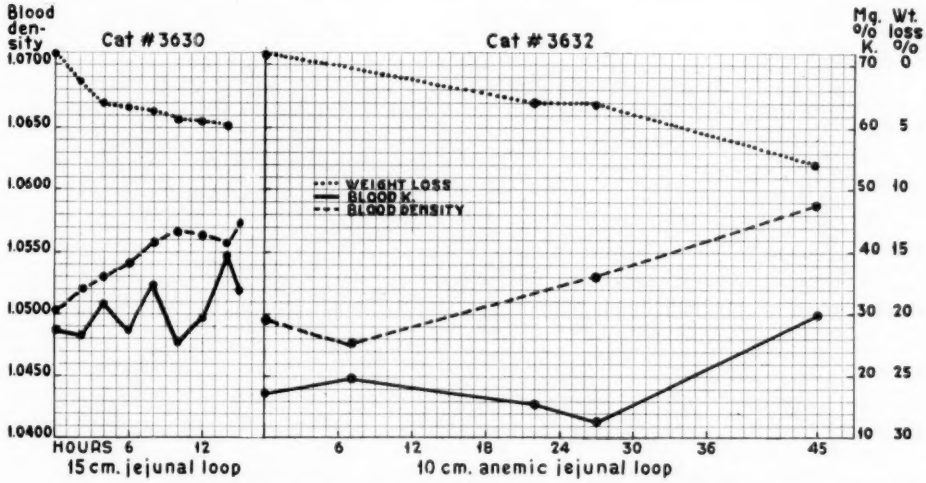

Fig. 1.—Cat 3630. Fifteen-centimeter jejunal loop obstructed between tapes. Survival 15 hours. Graph indicates decrease in weight, and rise in blood density. Two-hourly determinations of potassium show fluctuation above normal, with a 100 per cent increase before death. Loop contents: 77.2 mg. per cent potassium.

Cat 3635. Ten-centimeter anemic loop of jejunum between tapes. Survival 48 hours. Weight loss was 8.7 per cent. Fall in potassium to below normal, with a 50 per cent rise above normal during the last day of life. Rise in blood density preceded rise in potassium.

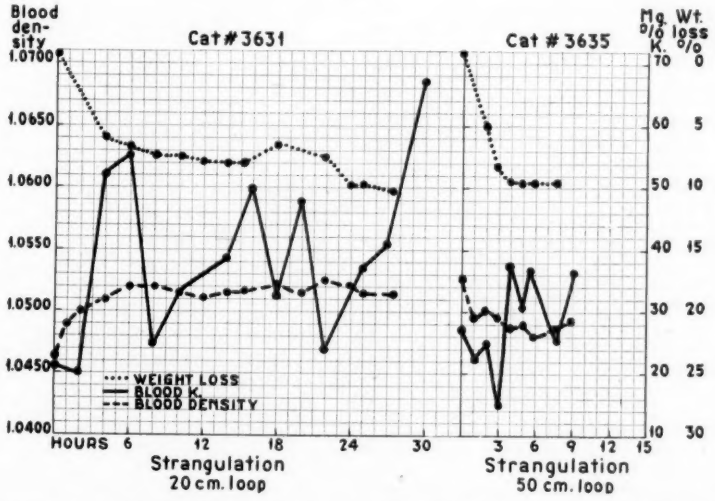

Fig. 2.—Cat 3631. Twenty-centimeter loop of jejunum strangulated by tape. Survival 30 hours. Progressive weight loss of 10.5 per cent. Blood density increased during first 6 hours and remained constant at this level. A 150 per cent increase in potassium during first 6 hours, followed by fluctuations with a rise to 230 per cent above normal during last 8 hours.

Cat 3635. Fifty-centimeter loop of jejunum and ileum strangulated by tape. Survival 9½ hours. Weight loss was 10.5 per cent. Fall in blood density with a slight terminal rise. Sharp fall in blood potassium during first 3 hours, with a mean level of 33.2 mg. per cent, representing a 65 per cent increase above normal during last 6 hours. Peritoneal fluid 63 mg. per cent. Loop contents 131.2 mg. per cent.

TABLE I

TYPES OF OBSTRUCTION WITH SURVIVAL TIME

1. Strangulation of a 50 cm. loop below the ligament of Treitz. Cat 3635.	9 hr.
2. Closed 15 cm. jejunal loop. Veins ligated. Mesentery cut to prevent collateral return. Arteries intact. Cat 3630.	15 hr.
3. Strangulation of 20 cm. jejunal loop below the ligament of Treitz. Cat 3631.	30 hr.
4. Closed 10 cm. jejunal loop with arteries and veins ligated. Lymphatics also blocked. "Anemic loop." Cat 3632.	48 hr.
5. Simple obstruction of esophagus at cardiac juncture. Cat 3636.	80 hr.
6. Simple obstruction of duodenum 3 cm. below ampulla of Vater. Cat 3639.	124 hr.
7. Simple obstruction of duodenum 2.5 cm. below ampulla of Vater. Cat 3638.	*176 hr.
8. Simple obstruction of transverse colon. Cat 3634.	†23rd day

*Killed at 176 hours, as cat was moribund.
†Abdomen opened on twenty-third day. Animal killed.

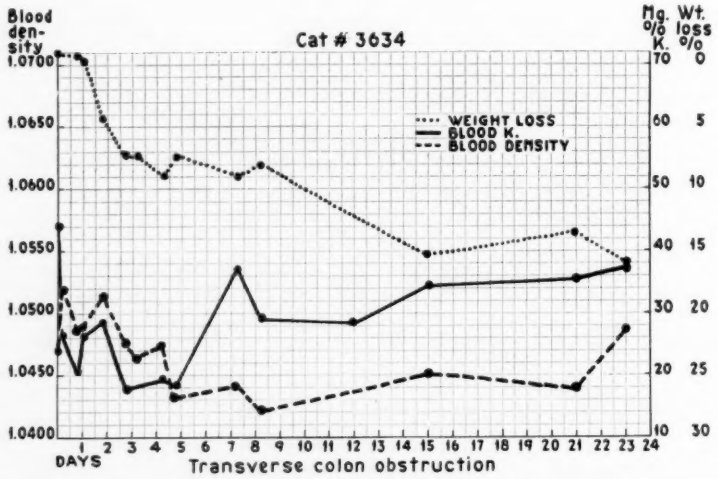

Fig. 3.—Cat 3634. Obstruction of transverse colon with tape. Abdomen reopened on twenty-third day, showing colon partially obstructed. This coincided with stools after the fourth day. Progressive decrease in weight, with a 17 per cent loss. Concentration of blood with subsequent dilution and a final increase in blood density. Blood potassium fell during first 5 days with a rise on the seventh day, followed by a level 75 per cent above normal.

In another cat (3632), a 10 cm. jejunal loop was formed between tapes as in the first experiment. The arteries, veins, and lymphatics were ligated, thus forming an anemic loop (see protocol). The survival time was 48 hours. The rise in blood density occurred sooner than the final rise in blood potassium. *Autopsy:* The loop was found to be black, not ruptured; the peritoneal fluid was reddish and abundant; the lungs were pink and collapsed; the heart was in diastole.

B. The two other animals of this group had strangulation of jejunal and upper ileal loops. In the first (3631) a 20 cm. jejunal loop was formed by ligating the base of the mesentery with tape. The constriction permitted arterial flow but not venous return. Blood potassium and density were followed hourly, and fluctuations in the former were marked. The blood density reached its peak in 6 hours and remained at this level until death. The weight fall was progressive except for one rise after giving the animal water. The terminal rise of potassium to 66 mg. per cent was the highest in this first group. Cat survived 30 hours.

Autopsy: Peritoneal fluid was abundant and reddish in color; the ligatured loop was distended and filled with reddish, foul fluid; the color of the mesentery and intestine was greenish black; the small intestine below the obstruction was collapsed; the stomach and duodenum were markedly distended; there was no peritonitis.

In Cat 3635, strangulation of a 50 cm. loop of jejunum and ileum was effected by means of a tape passed around the base of the mesentery, permitting arterial inflow but preventing venous return. Blood potassium and density were followed hourly. The latter fell rapidly during the first six hours, with a terminal small concentration. The potassium fell from an initial value of 27.7 mg. per cent to below normal by the third hour; it then rose to 37.6 mg. per cent and fluctuated

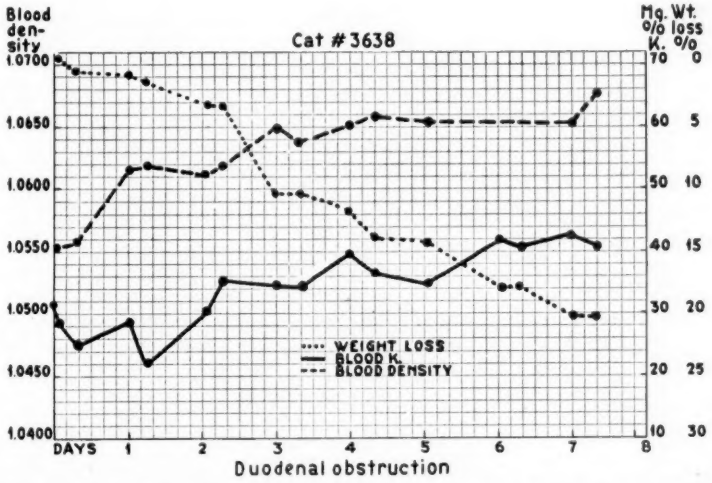

Fig. 4.—Cat 3638. Duodenal obstruction. Killed at 176 hours, as it was moribund. Weight loss was 21.2 per cent. Gradual rise in density during first 3 days. This increase was maintained until the end. Fall in potassium preceded a progressive fluctuating rise to levels over 100 per cent above normal during last 36 hours.

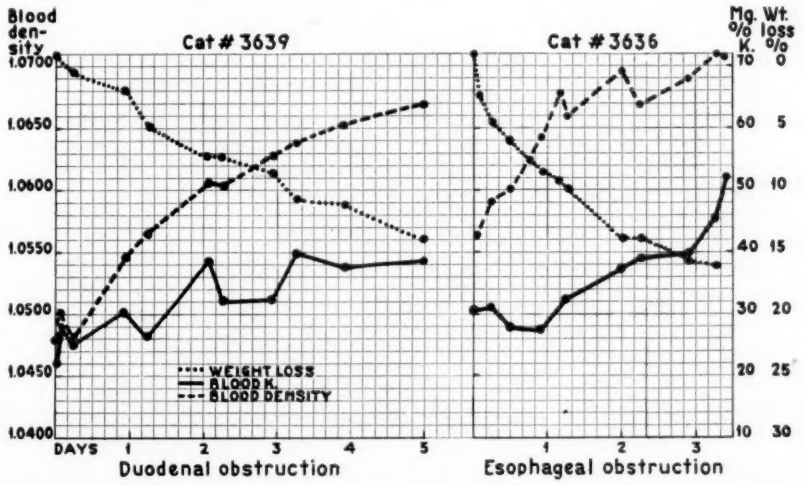

Fig. 5.—Cat 3639. Duodenal obstruction by tape below ampulla of Vater. Survival 128 hours. Weight loss was 15 per cent. Sustained rise in blood density. Fluctuating increase in blood potassium to levels 100 per cent above normal during the last 48 hours. Vomitus 254 mg. per cent. Blood potassium at this time 38.5 mg. per cent.
Cat 3636. Esophageal obstruction at cardiac juncture. Survival 80 hours. Weight loss was 17 per cent. Rapid increase in blood density. Fall in potassium followed by a sustained rise to 160 per cent above normal.

in this high range until death. The course of symptoms was rapid, with profuse vomiting, prostration, air hunger, and a terminal generalized convulsion just before death. The survival time was 9 hours. Peritoneal fluid removed immediately after death had a potassium content of 63 mg. per cent, while that of the contents of the obstructed loop was 131 mg. per cent. *Autopsy:* Peritoneal cavity contained a greenish red fluid; the ligated loop was distended and filled with a foul reddish black fluid; the intestines below the obstruction were contracted; proximal duodenum and stomach were dilated; the lungs were collapsed, pink, and showed no consolidation; the heart was in diastole and practically empty of blood.

Group II includes cats with *simple obstruction* at different levels.

A. The transverse colon of Cat 3634 was obstructed by ligature with tape. Blood potassium and density were determined twice daily for 4 days; daily for 4 days; and then every fourth day until the abdomen was reopened on the twenty-third day. Inspection of the colon showed hypertrophy and dilatation of the proximal part. The patency of the bowel had partly reestablished itself, permitting the introduction of a probe at the site of obstruction. There was a concentration of the

PROTOCOL 1

Cat 3630. Male. Weight, 3.543 Kilos. Closed Jejunal Loop, 15 cm., With Veins Ligated and Mesentery Cut so as to Prevent Collateral Venous Circulation. Arteries Intact.

DATE	TIME	TIME AFTER OP.	CONDITION AND REMARKS	WEIGHT % LOSS	BLOOD DENSITY	BLOOD K MG.%
Aug.						
15	1:00 P.M.	0	Good	–	1.0486	–
16	10:00 A.M.	0	Good	–	1.0524	–
17	1:00 P.M.	0	Good	–	1.0502	27.5
	2:10 P.M.		Obstructed under ether	2.4	1.0521	26.3
	4:25 P.M.	2 hr.	Recovered; vomited twice			
	6:20 P.M.	4 hr.	Vomited; listless; blood sample from ear	3.0	1.0528	31.8
	8:30 P.M.	6 hr.	Sitting with head down; wound bulging; blood sample from ear	3.2	1.0542	27.6
	10:30 P.M.	8 hr.	Crouching; hind leg weakness; sample of blood from ear	3.6	1.0558	32.3
18	12:30 A.M.	10 hr.	Walks with unsteady gait; diarrhea; blood sample from ear	4.1	1.0565	25.0
	2:30 A.M.	12 hr.	Lying down; dry skin; hind leg weakness; peripheral blood very thick and scanty; heart blood had to be taken; water given	4.4	1.0564	28.7
	4:30 A.M.	14 hr.	Temp. 96° rectal; resp. 120; lying stretched out; does not respond to sudden loud noise; blood samples from ear and heart	4.8	1.0558	39.3
	5:15 A.M.	15 hr.	Grunting respiration; twitching of legs; unsteady gait; slight convulsion; peripheral blood not obtained; heart blood	4.8	1.0573	33.8
	5:18 A.M.		Dead. Loop contents at autopsy. 77.2 mg. % K			

Autopsy: Loop black, not ruptured; reddish peritoneal fluid; contents of loop brownish red. Lungs collapsed. Heart in diastole. Bladder distended.

blood for forty-eight hours, with a subsequent dilution. This was paralleled by a rise and fall in potassium. On the fourth day after the operation the general condition of the cat suddenly improved, which was coincident with the passage of a stool, signifying reestablishment of the continuity of the alimentary tract.

B. Cat 3638 had its duodenum obstructed 2.5 cm. below the ampulla by means of a tape. Potassium and density were determined twice daily. The train of symptoms developed slowly. Vomiting occurred only twice during the first forty-eight hours. Prostration was marked during the last two days, and moderate bleeding from the buccal cavity was observed. The animal was killed after 176 hours, as it was moribund. The rises in potassium and density were practically constant. *Autopsy:* A greatly dilated stomach and duodenum; collapsed small intestine; there was no peritoneal fluid nor sign of inflammation; the lungs were pink, collapsed, and free from consolidation; the heart was in diastole; weight loss 21.2 per cent.

The duodenum was obstructed 3 cm. below the ampulla of Vater in Cat 3639, as in the previous cat. Blood potassium and density were followed twice daily. The rises in potassium and density were practically parallel. Vomiting occurred more frequently than in Cat 3638. A sample of vomitus taken 120 hours after ligation contained 254 mg. per cent of potassium, at a time when the blood potassium was 38.5 mg. per cent. Survival 130 hours. Weight loss 14.9 per cent.

C. In Cat 3636, the esophagus was ligated through an upper midline abdominal incision at its juncture with the cardia. The postoperative course was punctuated with repeated vomiting of frothy fluid. The rise in potassium was the most constant in this experiment, and the blood density reached its highest figure. The

PROTOCOL 2

Cat 3632. Female. Weight, 3.572 Kilos. Closed Jejunal Loop, 10 cm. With Arteries and Veins Tied. "Anemic Necrosis."

DATE	TIME	TIME AFTER OP.	CONDITION AND REMARKS	WEIGHT % LOSS	BLOOD DENSITY	BLOOD K MG.%
Aug.						
8	12:30 P.M.	0	Good; blood from ear	–	1.0484	–
9	12:30 P.M.	0	Good; blood from ear	–	1.0479	–
10	1:00 P.M.		Active and healthy; blood sample from ear	–	1.0496	17.3
	1:30 P.M.		Obstructed by tapes under ether			
	1:45 P.M.	15 min.	Blood from ear		1.0500	–
	5:05 P.M.		Breathing rapidly, 120; vomited; refuses fluid			
	8:30 P.M.	7 hr.	Blood sample from ear		1.0477	19.5
11	8:00 A.M.		Lies on side; refuses food; respirations slower, 50			
	11:15 A.M.	22 hr.	Blood sample from ear	3.9	–	15.9
	4:30 P.M.	27 hr.	Hind legs weak; tumor mass felt in abdomen; vomited; blood sample from ear	4.0	1.0533	12.5
	6:00 P.M.		Vomited blackish fluid			
	8:45 P.M.		Urinated; resp. 74			
12	9:00 A.M.	45 hr.	Unable to stand; vomited during night; resp. 72	8.7	1.0587	29.6
	12:15 P.M.	47 hr.	Lying stretched out; body cold; unable to raise head; vomited			
	4:15 P.M.		Found dead			

Autopsy: Loop black; not ruptured; peritoneal fluid abundant and reddish in color. Stomach dilated. Intestines collapsed; large bowel filled with hard feces. Thoracic cage contained no fluid; lungs collapsed, pink. Heart in diastole. Kidneys pale, tense, and swollen. Bladder distended. Adrenals soft; tan color.

weight loss was 17.1 per cent. Death in coma after 80 hours. *Autopsy:* No evidence of peritonitis; stomach, small intestine, and large intestine were collapsed; the obstruction was complete at the cardiac end of stomach; esophagus dilated; lungs pink and collapsed, no consolidation.

In these experiments, intestinal obstruction was associated with a rise in blood potassium to levels which have been shown to be toxic.[5] In the animals with strangulation the high levels were reached within a few hours. The two cats with duodenal obstruction evidenced a steady rise in potassium. The animal with esophageal obstruction, however, gave the most consistent and sustained rise. There was hemoconcentration in all the experiments save the one in which a 50 cm. loop of the upper intestine had been strangulated. This may be ascribed to considerable loss of blood into the loop. The greatest increase in blood density was manifested in esophageal obstruction.

PROTOCOL 3

Cat 3631. Male. Weight, 3.686 Kilos. Strangulation of 20 cm. Loop of Jejunum and Upper Ileum

DATE	TIME	TIME AFTER OP.	CONDITION AND REMARKS	WEIGHT % LOSS	BLOOD DENSITY	BLOOD K MG.%
Aug.						
15	10:00 A.M.	0	Good		1.0482	19.1
16	9:30 A.M.	0	Good; blood sample from ear		1.0488	
17	1:00 P.M.	0	Blood sample from ear		1.0461	21.2
			Operation ended 2:30 P.M. *Duration 15 min.*			
	3:30 P.M.	1 hr.	Vomited once, on coming out of ether and again 1 hr. later		1.0492	
	4:30 P.M.	2 hr.	Blood sample from ear		1.0500	20.1
	6:40 P.M.	4 hr.	Vomited; restless; wound bulging	7.0	1.0509	52.3
	8:30 P.M.	6 hr.	Prostrated; hind leg weakness; blood sample from ear	7.7	1.0522	55.8
	10:30 P.M.	8 hr.	Prostrated; abdomen bulging	8.1	1.0519	24.2
18	12:50 A.M.	10⅓ hr.	Abdomen now tightly distended; blood sample from ear	8.5	1.0516	33.2
	2:45 A.M.	12 hr.	Hind leg weakness; blood sample from ear	8.9	1.0511	
	4:30 A.M.	14 hr.	Rectal temp. 100.1°; resp. 48	8.9	1.0515	38.6
	6:00 A.M.	15 hr.	Prostrated; water given; drank greedily	9.0	1.0515	49.7
	8:30 A.M.	18 hr.	Abdomen tight; wound wet; legs weak; drinks water	7.3	1.0522	32.5
	10:30 A.M.	20 hr.	Lies on side		1.0514	46.9
	12:40 P.M.	22 hr.	Abdomen tight; legs weak	8.5	1.0524	22.0
	3:00 P.M.	24 hr.	Body cold	10.9	1.0520	
	3:30 P.M.	25 hr.	Unable to get peripheral blood; heart blood	10.9	1.0515	36.5
	6:15 P.M.	28 hr.	No peripheral blood; heart blood	11.1	1.0514	40.9
	9:30 P.M.	30 hr.	Dead. Heart blood. Autopsy immediately			66.6

Autopsy: Peritoneal cavity filled with reddish fluid; strangulated loop distended, reddish black, and filled with foul reddish brown fluid. Loop not ruptured. Intestine below obstruction collapsed. Colon contracted and filled with solid fecal material. Stomach and duodenum dilated. Liver had nutmeg appearance and was soft. Spleen leathery. Kidneys brownish yellow and soft. Adrenals pale. Lungs collapsed and pink; free from consolidation. Heart in diastole. Urinary bladder distended.

DISCUSSION

The results described in the present paper are in conformity with those of Murphy and Vincent[8] and others,* who found that animals with simple obstruction lived longer than those with interference of the vascular supply, and that the survival time in the latter varied inversely with the length of the occluded loop. In simple obstruction in experimental animals and in human beings, the higher the location of the lesion in the alimentary tract, the more rapid is the lethal outcome.[9]

Amussat[10] was the first to suggest that intestinal obstruction led to a general toxemia, and many subsequent workers have produced evidence in support of this view, particularly when strangulation is a complicating factor. The theories regarding the chemical nature of toxic substances are too diversified to be discussed in detail. One

PROTOCOL 4

Cat 3635. Male. Weight, 2.779 Kilos. Strangulation of 50 cm. Loop of Jejunum and Ileum

DATE	TIME	TIME AFTER OP.	CONDITION AND REMARKS	WEIGHT % LOSS	BLOOD DENSITY	BLOOD K MG.%
Sept. 2	10:00 A.M.	0		2.779	1.0526	27.7
	1:10 P.M.		Operation ended; duration 15 min.			
	2:10 P.M.	1 hr.	Vomited salmon; blood from ear		1.0492	22.2
	3:25 P.M.	2 hr.	Vomited several times; blood sample from ear	6.1	1.0501	25.5
	4:25 P.M.	3 hr.	Body cold; prostrated; vomited much undigested food; blood sample from ear	9.3	1.0495	17.3
	5:24 P.M.	4 hr.	Hard distended loops felt; prostrated; still vomiting	10.2	1.0486	37.6
	6:25 P.M.	5 hr.	Bulging coils of intestine felt; prostrated; cold	10.2	1.0489	30.2
	6:55 P.M.	6 hr.	Lying on side; quiet; blood sample from ear	10.2	1.0479	36.6
	8:55 P.M.	8 hr.	Body cold; air hunger	10.5	1.0485	25.0
	10:20 P.M.	9 hr.	Air hunger marked; heart blood taken, as peripheral blood scanty		1.0492	36.4
	10:30 P.M.		Died after generalized convulsion			
			Autopsy done at death. Peritoneal fluid			63.0
			Contents of loop			131.2

Autopsy: The peritoneal fluid was abundant and reddish in color; ligatured loops distended and filled with reddish foul fluid; diameter of loop 2 cm. Mesentery and intestine were greenish black. Loop not ruptured. No peritonitis. Small intestine below obstruction collapsed. Stomach and duodenum markedly distended. Spleen shrunken. Liver had nutmeg appearance. Kidneys pale, large, and soft. Adrenals pale. Lungs collapsed, pink, and free from consolidation. Heart in diastole. Bladder distended.

*A more complete discussion and bibliography are given by Cooper, H. S. F.: Cause of Death in High Obstruction, Arch. Surg. **17**: 918, 1928.

McIver, M. A.: Acute Intestinal Obstruction, New York, 1934, Paul B. Hoeber, Inc.

school, headed by von Albeck,[11] holds that the toxin is diffusible, while Kukula,[12] on the other hand, stated that the Chamberland filter removed it. Murphy and Vincent concluded that the toxic substance is destroyed by boiling, is insoluble in water, and will not pass a Berkefeld filter. In their investigation of toxic fluid from the peritoneal cavity, Aird and Henderson[13] found at least two distinct toxic substances: one a complex protein of the euglobulin type, probably of bacterial origin, and the other, a dialyzable substance of the nature of histamine. The apparent histamine content of the transudate, tested pharmacologically on rat's uterus and on guinea pig's ileum, increased steadily in the first twenty-four hours. Slome and Knight[14] excluded the possibility of the latter substance's being either histamine or acetylcholine, but confirmed the finding that the peritoneal fluid in cases of strangulation was, at the end of twenty-four hours, definitely toxic. It is of interest that Van Beuren[15] demonstrated that the normal intestinal contents and mucosa were also toxic to laboratory animals.

Hartwell and Hoguet[16] questioned the idea of toxemia and were first to formulate a definite theory that death from obstruction was due

PROTOCOL 5

Cat 3634. Male. Weight, 3.2 Kilos. Obstruction of Transverse Colon

DATE	TIME	TIME AFTER OP.	CONDITION AND REMARKS	WEIGHT % LOSS	BLOOD DENSITY	BLOOD K MG.%
July 15			Fasting sample from ear			21.2
Aug. 10	1:50 P.M.	0	Blood sample from ear after a meal		1.0470	42.0
	2:07 P.M.		*Obstruction of transverse colon ended*			
10	2:15 P.M.	15 min.	Not recovered		1.0518	
	8:40 P.M.	6½ hr.	Blood sample from ear			26.3
11	11:10 A.M.	21 hr.	Drank water and milk	0.4	1.0485	20.4
	4:45 P.M.	26½ hr.	Urinated; blood from ear	0.6	1.0486	26.2
	6:10 P.M.	28 hr.	Vomited brownish fluid		1.0488	
12	9:00 A.M.	43 hr.	Refuses water and milk	5.4	1.0513	28.3
	5:15 P.M.	51 hr.	Refuses water and milk		1.0485	
13	9:15 A.M.	67 hr.	Hind leg weakness apparent	8.2	1.0474	17.8
	5:10 P.M.	75 hr.	Refuses food and water		1.0563	
14	9:00 A.M.	105 hr.	Drank milk	10.0	1.0475	19.4
	12:30 P.M.	108 hr.	Passed a stool; condition during afternoon changed			
15	9:00 A.M.	129 hr.	Very alert; eats	8.2	1.0434	18.3
17	9:00 A.M.	7 days	Vomited several times; diarrhea	10.0	1.0442	36.9
18	9:30 A.M.	8 days	Eats	8.9	1.0420	29.0
22	9:30 A.M.	12 days	Active; very thin			28.5
25	9:30 A.M.	15 days	Stools watery, yellow	16.3	1.0452	34.6
31	9:30 A.M.	21 days	Eats; active; stools	14.5	1.0440	35.6
Sept. 2	12:05 P.M.	23 days	Thin and scrawny	17.0	1.0486	37.3

The abdomen was opened under anesthesia. Peritoneal cavity dry; several omental adhesions about site of ligature. Proximal colon hypertrophied and dilated 2 cm. in diameter. The obstruction was 10 cm. caudad from the ileocecal valve. On opening the bowel, a probe could be passed through the partial occlusion.

to loss of digestive secretions, a conception elaborated upon by numerous subsequent workers. There exists, however, a twofold objection to the conclusions of these authors. First, in rabbits which do not vomit, the continued removal of accumulated secretions in the stomach from these animals with jejunal obstruction and the administration of sodium chloride practically double the survival period.[17] Second, in animals with esophageal obstruction, the same clinical course and the same biochemical findings are present in an even more striking form than in high intestinal obstruction. Workers who explain death in simple obstruction on a water or electrolyte depletion basis admit,

PROTOCOL 6

Cat 3638. Male. Weight, 4.818 Kilos. Obstruction of Duodenum 2.5 cm. Below the Ampulla of Vater

DATE	TIME	TIME AFTER OP.	CONDITION AND REMARKS	WEIGHT % LOSS	BLOOD DENSITY	BLOOD K MG.%
Sept. 21	10:15 A.M.	0	Strong, healthy; blood sample obtained after much struggling		1.0554	31.7
	10:30 A.M.		Operation			
	12 NOON	1½ hr.	Recovered; still resists; urinated	0.6	1.0553	28.5
	6:15 P.M.	8 hr.	Blood sample from ear; refused milk and water	1.4	1.0557	25.5
	7:15 P.M.		Stool			
	12 MIDNIGHT		Lying stretched out; quiet			
22	10:50 A.M.	24 hr.	Resisted taking blood; refuses salmon, milk, and water	1.7	1.0615	28.7
	5:50 P.M.	30 hr.	Still resists when blood is drawn; abdomen distended; violent vomiting.	2.4	1.0617	21.8
	8:00 P.M.		Cage drenched with brownish fluid			
23	12:30 P.M.	50 hr.	Blood sample from ear	4.1	1.0611	30.3
	5:45 P.M.	55 hr.	Blood sample from ear; quiet	4.1	1.0617	35.2
24	8:45 A.M.		Vomited brownish fluid			
	10:20 A.M.	72 hr.	Blood sample from ear; refuses milk and water	11.2	1.0651	34.5
	5:20 P.M.	79 hr.	Blood from ear; hind leg weakness	11.2	1.0638	34.3
25	7:00 A.M.		Vomited during night			
	10:20 A.M.	96 hr.	Blood from ear; refused salmon	12.7	1.0652	39.7
	2:00 P.M.		Hind leg weakness; urinated			
	6:45 P.M.	104 hr.	Blood from ear; drank water	14.7	1.0659	36.7
26	6:30 A.M.		Lying stretched out and limp			
	11:20 A.M.	121 hr.	Abdomen distended; blood from ear	15.3	1.0654	34.8
27	11:30 A.M.	145 hr.	Blood taken from ear	18.8		42.0
	6:00 P.M.	151 hr.	Blood taken from ear	18.8		40.9
28	11:15 A.M.	169 hr.	Blood from ear; tongue bloody	21.2	1.0653	42.6
	6:15 P.M.	176 hr.	Vomited brownish fluid; blood taken from heart; animal killed, as it was moribund	21.2	1.0676	41.0

Autopsy: Stomach greatly dilated. Small intestine collapsed. No peritoneal fluid. Lungs collapsed. Heart in diastole. Kidneys tense and swollen. Adrenals pale. Urinary bladder distended.

however, that a new factor is added to the syndrome when the blood supply is impaired, this being associated with some form of toxemia.

These discordant views may be reconciled on the assumption that the condition is essentially one of *potassium* poisoning. This conclusion is based on our determination of blood potassium during the course of the entire syndrome in both simple and strangulated obstructions. Our experiments reveal toxic levels of blood potassium, which could, in themselves, be responsible for death.

In simple obstruction, the potassium rise can be ascribed to dehydration associated with loss of extracellular, and replacement by intracellular, fluids and electrolytes.[18] In strangulation, however, the picture is complicated by several factors. Obstruction, hemorrhage in

PROTOCOL 7

Cat 3639. Male. Weight, 3.799 Kilos. Simple Duodenal Obstruction 3 cm. Below Ampulla of Vater

DATE	TIME	TIME AFTER OP.	CONDITION AND REMARKS	WEIGHT % LOSS	BLOOD DENSITY	BLOOD K MG.%
Sept. 21	9:30 A.M.	0	Good condition		1.0478	21.8
			After operation			
	12:10 P.M.	40 min.	Blood sample from ear		1.0501	28.7
	1:30 P.M.		Recovered; sitting up			
	6:00 P.M.	6 hr., 40 min.	Condition good; refuses milk, salmon, and water	1.5	1.0479	25.2
	12 MIDNIGHT		Lying quietly; no vomiting			
22	7:05 A.M.		Vomited greenish fluid			
	10:20 A.M.	23 hr.	Blood sample from ear	2.9	1.0546	30.5
	11:40 A.M.		Urinated			
	2:40 P.M.		Vomited greenish fluid			
	5:45 P.M.	30½ hr.	Blood sample from ear	5.9	1.0565	26.1
	9:00 P.M.		Vomited greenish fluid			
23	5:30 A.M.		Sitting up; good resp. 72			
	8:40 A.M.		Vomited greenish fluid; drinks water freely			
	12:20 P.M.	49 hr.	Blood sample from ear	8.2	1.0606	38.5
	5:45 P.M.	54 hr.	Blood sample from ear	8.2	1.0604	32.0
	5:50 P.M.		Urinated; lying down with head up			
24	1:00 A.M.		Vomited			
	7:00 A.M.		Vomited between 1 and 7 A.M.			
	10:10 A.M.		Blood sample from ear	9.5	1.0627	32.3
	1:00 P.M.		Hind leg weakness			
	2:00 P.M.		Vomited foul-smelling, yellowish fluid twice			
	5:15 P.M.	78 hr.	Blood sample from ear; sitting all afternoon with head over water; does not drink; urinated; condition poor; body cold	11.9	1.0637	39.7
25	9:50 A.M.	95 hr.	Blood sample from ear	12.1	1.0652	37.5
	6:30 P.M.	103 hr.	Blood sample from ear; apathetic; lies on side	13.4	1.0646	
26	6:30 A.M.		Vomited during night			
	8:30 A.M.		Vomited; portion for analysis;			
	11:00 A.M.	120 hr.	blood sample from ear	14.9	1.0669	38.5
			Between 6 and 7 P.M. Died			

the loop, tissue necrosis, bacterial toxins, all contribute to the rapid demise of the animal, probably by effecting an earlier and sustained rise in blood potassium. This would involve the potassium-raising effect of dehydration, blood loss,[19-21] and the release of potassium from injured tissue cells. Toxins of bacterial origin, such as histamine, may also contribute to this rise in potassium, since it has been shown that injections of histamine will raise blood potassium.[22] The excess of potassium entering the blood stream might thus be satisfactorily accounted for as arising from the above-enumerated sources.

PROTOCOL 8

Cat 3636. Male. Weight, 3.6 Kilos. Esophageal Obstruction at Cardiac End of Stomach by Tape

DATE	TIME	TIME AFTER OP.	CONDITION AND REMARKS	WEIGHT % LOSS	BLOOD DENSITY	BLOOD K MG.%
Sept. 21	10:00 A.M.	0	Condition good		1.0503	30.0
	11:45 A.M.	0	Operation ended (15 min.)			
	12:30 P.M.	45 min.	Vomited frothy fluid		1.0563	20.8
	1:30 P.M.	1¾ hr.	Vomited frothy fluid 4 times in last hour; constant licking	3.2	1.0563	
	2:15 P.M.	2½ hr.	Restless; retching; vomited twice	3.2	1.0563	
	5:45 P.M.	6 hr.	Vomited twice; resp. 106	5.5	1.0591	30.8
	11:20 P.M.	11½ hr.	In past 5 hr. vomited twice; resp. varied from 34 to 83; refused milk and water; not so restless	7.1	1.0601	27.7
22	12:10 A.M.		Vomited twice; still restless; drank 4 oz. water			
	1:10 A.M.		Heart rate 106; resp. 40; vomited twice			
	5:40 A.M.	18 hr.	Lying limp in cage	8.9	1.0622	
	10:30 A.M.	22¾ hr.	Vomited twice; drank water	9.4	1.0641	27.5
	3:50 P.M.	28 hr.	Vomited twice; refused salmon; drank water and vomited	10.2	1.0678	
	5:40 P.M.	30 hr.	Vomited once; restless; retching; drinks little; sits with head over bowl; urinated first time since operation	11.0	1.0660	32.2
23	5:30 A.M.		Pulse 170; resp. 36			
	8:40 A.M.		Passed urine			
	12:15 P.M.	48½ hr.	Sits with head over bowl; body cold; hind leg weakness	14.9	1.0696	36.9
	5:15 P.M.	53½ hr.	Drinks water	14.9	1.0669	38.5
	11:20 P.M.		Vomited			
24	7:00 A.M.		Hind leg weakness			
	9:50 A.M.	70 hr.	Sits with head over bowl of water; drinks occasionally	16.6	1.0690	39.6
	11:30 A.M.		Vomited; lies stretched out;	17.1	1.0713	45.3
	5:15 P.M.	77½ hr.	body cold; difficult to rouse; pulse 120; resp. 14			
	8:15 P.M.	80½ hr.	Died in coma; last blood sample from vena cava		1.0709	52.0

Autopsy: No peritonitis. Stomach, small intestine, and colon contracted. Bladder distended. Liver and spleen shrunken. Kidneys pale and soft. Adrenals pale. On opening the stomach the obstruction at the cardia was found complete. Esophagus dilated. No fluid in thoracic cavity. Lungs collapsed, pink; free from consolidation. Heart in diastole.

CASE REPORT

P. H., No. 448619. Fifty-Year-Old Jewish Tailor. Weight, 73 Kilos

DATE	INTAKE	OUTPUT	WATER BALANCE	BLOOD DENSITY	R.B.C.	HG PER CENT	URINE SP. GR.	BLOOD CHEMISTRY	REMARKS
Sept. 24					5.04	93	1.035		Admitted with severe epigastric pain of 6 hours' duration. B. P. 115/85.
								Potassium mg. %	EK: Cardiac muscle damage.
25	2000	2850	- 850		4.68	90	1.030	Plasma 29.8; Whole Blood 202; Cells 365. Hematocrit: 47	X-ray of abdomen: "fluid levels."
26	2000	2775	- 1,625	1,0563‡	-	-	-		Op.: Enterostomy. EK: Def. muscle damage.
27	2100	4350	- 3,875				1.040		X-ray: "Fluid levels and mottling both bases."
28	5300	4390	- 2,965	1.0551				B.U.N.: 18 mg. %; Cl 504 mg.	Exploratory lap. Division of band. Oxygen tent.
29	3160	3930	- 3,735	1.0513	(After 200 c.c. 5% NaCl)				EK: Changing conditions in muscle.
30	3595	5000	- 5,140	1.0524			1.025	B.U.N.: 12 mg. %; CO_2 42 vol. %	
Oct. 1	5000	7950	- 8,090	1.0556					Profuse drainage fr. enterostomy.
2	4145	5600	- 9,545	1.0543	5.72	90		N.P.N.: 27 mg. %; ser. protein: 6.4%; CO_2 66 vol. %; Cl 542 mg. %. Serum *potassium: 17.2 mg. %;* Na 135.2 m. eq./L; Ca 4.3 m. eq./L.	

CASE REPORT—CONT'D

3	4490	5350	-10,405	1.0554					Clyses were stopped, as patient's urine was over 1,000 c.c. per day. Taking fluids per mouth.
4	1100	3650	-12,955						
5	1200	3400	-15,155	1.0552					Removed from oxygen tent.
6	2325	3100	-15,930						Went into collapse. Cyanotic, cold, and clammy. B.P. 98/68. Transfusion. Oxygen tent. Blood density taken 6 hours after collapse; second determination after 2,000 c.c. of saline by clysis.
7	3500	2700	-15,130	1.0618 1.0598					
8	3175	3100	-15,055	1.0575			1.022		X-ray: pneumonitis subsiding.
9*	5600	2500	-11,955	1.0555				B.U.N.: 8 mg. %	Removed from oxygen tent.
10	3250	2050	-10,755						Soft diet; 1 gm. NaCl t.i.d.
11	4250	2900	- 9,405	1.0567					Tongue still dry.
12	3600	2800	- 8,605						Feels weak; no appetite.
13	3875	3400	- 8,130						
14	3450	1500	- 6,180						Feels better
15	3400	3100	- 5,880					Blood chlorides 500 mg. %	
16	3400	3300	- 5,780	1.0556				*Potassium mg. %*	
17†	1900	3150	- 7,030					Plasma 17.6; Whole Blood 198; Cells 367; Hematocrit: 49	
18					5.22	86			Up in chair today.

Insensible loss from 9/25-10/8 figured at 2,000 c.c. per day; from 10/9-10/17 1,500 c.c. per day.
*Water content of soft diet estimated at 500 c.c. per day. (Coller and Maddock.[41, 42])
†Fluid loss 10 per cent of body weight. Actual weight loss 14 per cent of body weight.
‡Specific gravity of blood.[43]

It may be supposed that in the human subject the amount of potassium liberated from blood extravasated into a strangulated loop would be much higher than in cats or dogs. The potassium content of the erythrocytes in these animals differs little from that of their plasma, whereas the human red blood cells contain 400 mg. per 100 ml., or 20 times as much as the plasma.

The normal means of elimination of potassium is by renal excretion. Zwemer and Truszkowski[2, 4] first suggested that this function cannot be adequately carried out without the presence of the adrenal cortical hormone, and examination of the histologic appearance of the adrenal cortex in both clinical and experimental intestinal obstruction, indicated depletion of its hormone reserves according to Zwemer's[23] classification. Harrop et al.[24] have found that potassium retention is a prominent feature of corticoadrenal insufficiency. It is now suggested that high intestinal obstruction may, as far as potassium metabolism is concerned, be identified with adrenal insufficiency.

Although a major part in the regulation of the blood electrolyte levels is usually ascribed to the kidneys, there is evidence, in cases of renal insufficiency, that other means may be utilized to rid the body of injurious catabolites. Bliss,[25] Austin and Gammon,[26] and Ingraham and Visscher[27] have shown that in both dog and man, concentration of potassium in the gastric juice is higher than in blood. The last named authors, making simultaneous determinations in 24 dogs, showed the concentration of potassium in gastric juice to be, on the average, 2.7 times, and in extreme cases, 4 times greater than in plasma. In the case of Cat 3639, we found the vomitus to contain 254 mg. per cent of potassium when the blood level was 38.5 mg. per cent. Possibly, therefore, secretion of potassium into the gastric lumen followed by vomiting may be regarded as a part of an auxiliary or emergency mechanism for lowering blood potassium. An esophageal obstruction would therefore prevent this detoxifying function with consequent earlier death of the animal.

In this light, the removal of stomach contents by gastric or duodenal tube, together with the administration of saline, as advocated by Wangensteen[31] in intestinal obstruction, is wholly justified. McIver,* commenting on the use of duodenal drainage advocated in the treatment of distention, feels this to be one of the major advances of the past decade.[28-30]

The benefit of salt in the treatment of intestinal obstruction and of adrenal insufficiency may be explained by its action in lowering the concentration of potassium by blood dilution and favoring its excretion. Furthermore, Amberg and Helmholtz[32] protected guinea pigs by means of sodium chloride against experimental potassium poisoning, and Bunge[33] has demonstrated that sodium protects against large

*McIver, M. A.: Acute Intestinal Obstruction, New York, 1934, Paul B. Hoeber, Inc.

amounts of potassium in the normal diet. Of importance is Thaler's[22] contribution that intravenous saline solution lowered posthemorrhagic hyperpotassemia in cats. In rats with intestinal obstruction, Schnohr[34] found the survival period to be lengthened by administration of 10 per cent sodium chloride, and suggested that this salt facilitated the excretion of some "noxious product."

Recently, Heuer and Andrus have given cortical extract simultaneously with transfusion, thereby prolonging the lives of dogs receiving intravenous injections of aqueous extracts of closed intestinal loops.[35] Since corticoadrenal extract[36] lowers plasma potassium in both adrenalectomized and normal cats, and will protect normal mice and guinea pigs from fatal amounts of potassium,[2, 4, 37] the therapeutic value of this measure would appear to be due to its effect on blood potassium.

Aird[38] stated that the chloride, sodium, and potassium content of the blood is low in intestinal obstruction. In a case of low ileal obstruction (P. H., No. 448619), we found a value of 29.8 mg. per cent potassium before operation and two values of 17.2 and 17.6 mg. per cent after operative and saline therapy.

In conclusion, we wish to emphasize that a high blood potassium is not peculiar to intestinal obstruction, but may be expected in all conditions associated with rapid or continuous excessive entry of potassium into the blood stream.[39,40]

We wish to thank Dr. Fuge for his help in Group A of these experiments and Dr. David Polowe, of Paterson, N. J., for the donation of the apparatus for blood density determination.

SUMMARY

1. In 8 cats it has been found that acute intestinal obstruction (esophagus, duodenum, jejunum, and colon) is associated with a rise in blood potassium to levels which have previously been shown to be lethal. The potassium content of obstructed loops, peritoneal fluid, and vomitus was many times that of blood.

2. The potassium rise is ascribed to some combination of dehydration, tissue breakdown, and action of bacterial toxin, with consequent adrenal and renal dysfunction resulting in adequate potassium elimination. The blood density parallels the rise in most instances.

3. It is suggested that potassium is the dialyzable toxic factor sought for in acute intestinal obstruction.

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THE URINARY LOSS OF IODINE FOLLOWING TOTAL THYROIDECTOMY

GEORGE M. CURTIS, PH.D., M.D., AND LOUIS E. BARRON, M.D., WITH THE TECHNICAL ASSISTANCE OF NORMAN L. MATTHEWS, B.S.,
COLUMBUS, OHIO

(From the Department of Research Surgery, The Ohio State University)

TOTAL ablation of the thyroid gland as a therapeutic measure in the management of congestive heart failure or for the relief of angina pectoris has recently received wide attention. It was described in June, 1933, by Blumgart and his associates.[1] Reports of the principles involved and of the results obtained have subsequently appeared in the literature.[2-6] The rationale for the total thyroidectomy is based upon extensive investigation which reveals a direct relationship between the velocity flow of the blood and the basal metabolic rate. The experimental background from which the procedure developed has been fully presented by Blumgart.[7]

The therapeutic significance of total thyroidectomy has been amply discussed in other and more extensive reports.[8] We have performed the operation on 11 patients presenting various stages of cardiovascular disease. Save perhaps in one instance, so far as we were able to determine, the cardiovascular disease was not of thyrogenic origin. Our clinical results resemble in miniature those extensively described in larger series.[9] Along with our clinical studies, however, we have taken this unusual opportunity to investigate the iodine metabolism of these patients.[10] This investigation represents a continuation of studies concerning the relationship between the blood and urinary iodine and thyroid function.

Immediately following partial thyroidectomy for various forms of goiter there ensues a striking increase in the urinary excretion of iodine.[11] This eventually returns to normal. The significance of the blood iodine and of the daily loss of iodine in the urine has been demonstrated.[12, 13] The fact that iodine metabolism is closely related to thyroid function is securely established. As a consequence, it seemed desirable to determine the urinary loss of iodine preceding, immediately following, and subsequent to, total thyroidectomy in man. The purpose of this paper is to report the results of this investigation.

LITERATURE

Alexander Sturm[14] found a slight but definite increase in the urinary loss of iodine subsequent to total thyroidectomy in dogs. Curtis and Barron[10] noted a definite increase in the urinary excretion of iodine

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immediately following total thyroidectomy in man. This was associated with an immediate postoperative increase in the blood iodine, which then gradually decreased to about one-third the normal level.

The average normal daily loss of iodine in the urine, as determined on 12 of our University Hospital patients, ranges from 0.036 to 0.078 mg.,[15] and averages 0.051 mg. The urinary excretion of iodine of patients with toxic goiter is increased during the untreated preoperative period.[11-13] Immediately following partial thyroidectomy there ensues an even greater loss, which may reach 2.0 mg. during the first twenty-four hours postoperatively.[11] Investigation of the urinary excretion of iodine following other than thyroid surgery also reveals an immediate increase in the postoperative loss.[16] From these observations it appeared that at least part of this increased iodine loss was due to extrathyroid depletion.[11]

METHODS

The urinary excretion of iodine was determined on 6 patients upon whom total thyroidectomy was accomplished for various stages of cardiovascular disease. In the first 2, small fragments of thyroid tissue in the adherent zone at the tracheoesophageal sulcus were not removed in order better to protect the parathyroids and the recurrent laryngeal nerves. The total remnant of thyroid tissue in each of these 2 patients was estimated to be less than one gram. In the remaining 4, total thyroidectomy in its strict literal sense was accomplished with due consideration to the blood supply of the parathyroid glands,[17] and to the recurrent laryngeal nerves.

All patients were maintained in the Research Surgical Service of the University Hospital on a diet which omitted those foods known to be high in iodine. The observations of Cole, Curtis and Bone[18] present the iodine content of our usual hospital diet. The patients were maintained either at bed rest or on limited physical activity. *Iodine was not used or administered in any form throughout their hospitalization.*

The collection of the twenty-four-hour urine specimens was carefully supervised. Blood samples for blood iodine determinations were drawn in the morning, in the postabsorptive state. Determinations of the blood and urinary iodine were made after the method of Phillips and Curtis.[19] This is an adaptation of the von Fellenberg procedure.[20] A few urinary iodine determinations were made after Matthews' modification of the Leipert method.[21] All determinations were made in duplicate.

Brief histories of the patients studied are presented. They include the principal findings and the management of each patient. These are accompanied by tables and figures which present the urinary excretion of iodine.

CASE 1.—*Hypertension With Congestive Heart Failure* (Fig. 1). A. W., a housewife, aged fifty-five years, entered the University Hospital on Oct. 12, 1933, for the management of hypertension with congestive heart failure. Dyspnea, weakness, palpitation, and precordial pain had been experienced intermittently for about two years. Respiratory distress was apparent on physical examination. A small hard nodule was palpated in the lower right lobe of the thyroid, which seemed otherwise normal. The physical findings were those of severe cardiac damage and congestive heart failure. Electrocardiographic studies revealed left ventricular preponderance. The blood pressure varied between 160/70 and 180/94. The trachea and larynx were normal.

Laboratory investigation revealed negative Wassermann and Kahn tests. A mild anemia was present. The white blood cells and differential counts were normal.

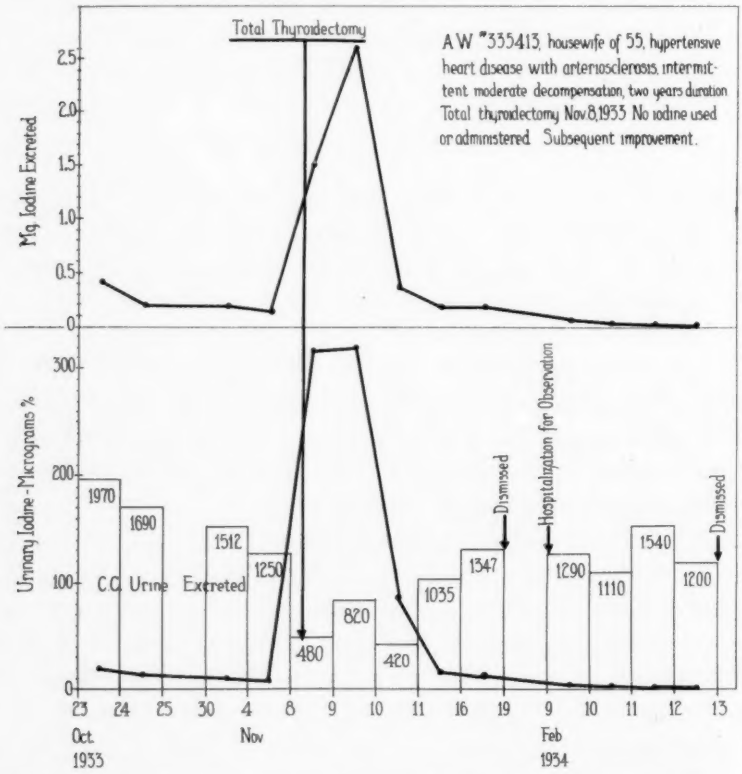

Fig. 1.—The urinary excretion of iodine following total thyroidectomy.

A trace of albumin and an occasional granular cast were observed on repeated urine examinations. Kidney function tests were within normal range. The blood N. P. N. was normal. The basal metabolic rate was plus 27, with the temperature 97.4°, the pulse 77, the respirations 23, the blood pressure 166/92, and the weight 118 pounds in the basal state.

During the preoperative period the daily urinary excretion of iodine ranged from 66 to 408 (0.066 to 0.408 mg.), and averaged 210 micrograms (0.210 mg.). The initial blood iodine was definitely increased to 55 micrograms per cent. It decreased during the preoperative period of preparation so that on the morning of operation it was 13.5 micrograms per cent. *No iodine was used or administered.*

Total thyroidectomy was accomplished on Nov. 8, 1933, using a basal anesthetic of avertin (80 mg. per kilogram) supplemented by local (novocaine ½ per cent) and

some gas (nitrous oxide) anesthesia. During the subsequent forty-eight hours there ensued a great increase in the urinary loss of iodine, Fig. 1. This rose to 2.6 mg. Subsequently, it gradually decreased, but was elevated at the time of dismissal from the hospital. The average daily urinary iodine excretion during the first eight postoperative days was 711 micrograms (0.711 mg.). For the entire postoperative period of eleven days, it averaged 553 micrograms (0.553 mg.).

The entire thyroid gland as removed weighed 40 grams. Within the lower right lobe there was one small colloid nodule. The remainder appeared to be normal. The microscopic appearance was normal. The iodine content of the whole gland was 24 mg. per cent, or 9.6 mg.

On Nov. 17, 1933, nine days after total thyroidectomy, the basal metabolic rate was plus 13, with the temperature 98.6°, the pulse 65, the respirations 21, the blood pressure 178/100, and the weight 123 pounds in the basal state. The blood iodine was 14.6 micrograms per cent. There were no complications. Convalescence was attended by considerable and definite symptomatic improvement. The patient was dismissed from the hospital on Nov. 19, 1933.

She was readmitted on Feb. 8, 1934, for investigation of the late results of total thyroidectomy. At this time observations on the blood and urinary iodine, the basal metabolic rate, and the clinical progress were made during a five-day period. There was definite clinical improvement. The daily urinary iodine loss ranged from 13 to 72 micrograms and averaged 39. The basal metabolic rate was minus 5, with the temperature 97°, the pulse 73, the respirations 19, the weight 131 pounds, and the blood pressure 198/120 in the basal state. The blood iodine averaged 1.6 micrograms per cent. The blood pressure fluctuated around 180/100.

Comment.—The average daily loss of iodine in the urine during the preoperative period was increased. Immediately following total thyroidectomy there ensued a greater increase. This persisted for about forty-eight hours and then gradually decreased. At the time of dismissal, however, it was still increased. Three months subsequent to total thyroidectomy, the urinary excretion of iodine was at a low normal range. At that time the blood iodine was the lowest we have thus far determined in man.

CASE 2.—*Hypertension of Unknown Etiology* (Fig. 2). E. K., a white housewife, aged thirty-eight years, entered the University Hospital on Oct. 26, 1933, for the management of "essential hypertension." Severe headaches with disturbance of vision had been present during the past twelve years. Frequent medical examinations revealed a persistent severe hypertension, averaging 230/130. There had been no clinical evidence of cardiac failure. Evidence of cardiac decompensation could not be obtained either by physical examination or by electrocardiographic studies. The trachea and larynx were normal. Ophthalmologic examination revealed old retinal hemorrhages.

Laboratory investigation revealed negative Wassermann and Kahn reactions. A mild anemia was present. The white blood cells and differential counts were normal. The serum calcium, phosphorus, and the nonprotein nitrogen of the blood were also normal. The kidney function tests were within normal range. The basal metabolic rate was plus 5, with the temperature 98.6°, the pulse 76, the respirations 14, the blood pressure 204/128, and the weight 124 in the basal state. *No iodine was used or administered.* The initial blood iodine was elevated, being 41 micrograms per cent. With dietary regulation and hospital bed rest it decreased to normal, Fig. 2. The preoperative average was 17.5 micrograms per cent. The urinary iodine ranged from 28 to 176 micrograms, averaging 77 micrograms daily.

Total thyroidectomy was accomplished on Nov. 21, 1933, using avertin (80 mg. per kilogram) supplemented by local anesthesia (½ per cent novocaine). There were no immediate or remote complications. The gland removed weighed 20 grams. Except for a small nodule at the posterior right pole, it was normal. The thyroid gland contained 98 mg. per cent iodine (dry basis) which is subnormal.

During the twenty-four hours subsequent to total thyroidectomy, there ensued a great increase in the urinary excretion of iodine. This increased to 2.5 mg. and then gradually subsided. The average daily postoperative loss of iodine for the first eight days was 547 micrograms. For the entire postoperative period it was 184 micrograms. The basal metabolism subsequently fell to minus 12, with the tempera-

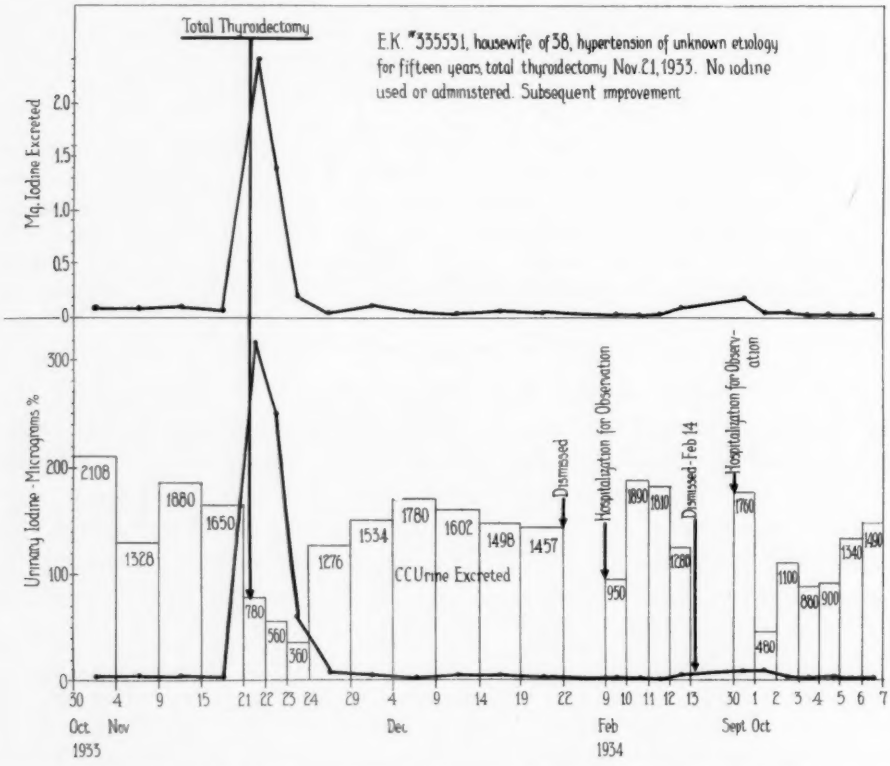

Fig. 2.—The urinary excretion of iodine following total thyroidectomy.

ture 97.8°, the pulse 65, the respirations 12, the weight 126 pounds, and the blood pressure 230/130. She was dismissed on Dec. 22, 1933, symptomatically improved.

She was readmitted on Feb. 8, 1934, for further investigation. There was definite evidence of myxedema. The blood pressure had returned approximately to its original level; however, symptomatic improvement still persisted. The basal metabolic rate was minus 25, with the temperature 98°, the pulse 63, the respirations 12, the blood pressure 190/130, and the weight 131 pounds in the basal state. The blood iodine averaged 6.0 micrograms per cent. The daily urinary iodine ranged from 22 to 72 micrograms and averaged 36. She was dismissed on Feb. 17, 1934.

She entered the hospital again on Sept. 29, 1934, for investigation of the late results of total thyroidectomy. During an eight-day period the daily urinary iodine

loss ranged from 20 to 174, averaging 51 micrograms. Myxedema was present. The basal metabolic rate was minus 21, with the temperature 98°, the pulse 68, the respirations 12, the weight 127 pounds, and the blood pressure 210/136 in the basal state.

Comment.—The preoperative urinary loss of iodine did not reveal the great variability observed in the preceding patient. Although some determinations were definitely elevated, the average daily excretion was at the upper limit of normal. During the twenty-four hours subsequent to thyroidectomy, there ensued a marked increase in the concentration of iodine in the urine. This gradually subsided, but was definitely increased at the time of the first dismissal from the hospital. Frequent subsequent determinations of the urinary iodine revealed low normal values.

CASE 3.—*Hypertension of Unknown Etiology* (Table I). H. G., a railroad fireman, aged forty-one years, entered the University Hospital on Apr. 3, 1934, for the management of "malignant hypertension." Nervousness, tinnitus, vertigo, and dyspnea had been present for about a year. Physical examination at the dispensary in September, 1933, revealed a severe hypertension. After admission to the hospital the blood pressure fluctuated around 210/140. The heart was moderately enlarged. No evidence of congestive heart failure was detected.

TABLE I

HYPERTENSION OF UNKNOWN ETIOLOGY OF ONE YEAR'S DURATION (CASE 3)

DATE	24-HOUR URINE VOLUME (C.C.)	IODINE MICROGRAMS %	IODINE EXCRETED IN MG.	BLOOD IODINE MICROGRAMS %	B. M. R. AND REMARKS
4/ 4/35	----	----	----	19.0	Plus 15
4/ 9/35	----	----	----		Plus 0
4/11/35	730	15.4	0.112		
4/12/35	1160	4.3	0.050	33.0	
4/13/35	1240	4.4	0.055		
4/14/35	----	----	----		
4/15/35	900	14.4	0.130		
4/16/35	1800	5.5	0.099	30.0	
4/17/35	2880	3.0	0.086		
4/18/35	1990	3.0	0.060	12.7	Minus 12
4/19/35	----	----	----	20.0	Preoperative
		TOTAL THYROIDECTOMY, APRIL 19, A.M.			
4/19/35	440	370.0	1.630	54.0	1 hr. postoperative
				29.0	3 hr. postoperative
				57.0	6 hr. postoperative
4/20/35	470	860.0	2.010	29.0	24 hr. postoperative
				13.1	30 hr. postoperative
4/21/35	880	121.0	1.070		
4/22/35	1760	23.0	0.400		
4/23/35	1650	6.8	0.112	11.3	
4/24/35	1490	2.4	0.036		
4/25/35	880	11.3	0.099	6.3	
4/26/35	870	5.5	0.048		Minus 10
4/27/35	1640	2.6	0.043	4.6	
4/28/35	1680	3.3	0.056		
4/29/35	1440	4.2	0.060	4.1	
		Dismissed April 30, 1934			

Laboratory investigation revealed negative Wassermann and Kahn reactions. The urine on repeated examinations was normal. There was no disturbance in kidney function. The nonprotein nitrogen of the blood was 32 mg. per cent. No abnormality was noted in other chemical analyses of the blood. The trachea and larynx were normal. The basal metabolic rate was plus 15, with the temperature 98.6°, the pulse 66, the respirations 11, the weight 179 pounds, and the blood pressure 184/92, in the basal state. *No iodine was used or administered.*

The blood iodine was increased but with adequate bed rest and dietary regulation this soon fell to normal, 12.7 micrograms per cent. The urinary iodine varied from 10 to 130, averaging 75 micrograms daily.

Total thyroidectomy was performed on Apr. 19, 1934, using avertin (80 mg. per kilogram) supplemented by local and gas anesthesia. There were no immediate or remote complications. The thyroid gland weighed 15 grams. Two small calcified nodules were found upon section. Otherwise the gland was normal. The whole gland contained 25 mg. per cent, or 3.8 mg. of iodine.

During the first twenty-four hours subsequent to total thyroidectomy, the urinary iodine increased to 1.6 mg. It subsequently gradually decreased and reached a normal range before the patient's dismissal from the hospital. The average daily urinary excretion of iodine for the first eight days postoperative was 672 micrograms. For the entire postoperative period of eleven days it averaged 464 micrograms. Associated with the immediate postoperative increase in the urinary iodine, there occurred a simultaneous increase in the blood iodine to 57 micrograms per cent (Table I). It then gradually decreased and eventually fell as low as 4.1 micrograms per cent (Table I).

Comment.—Although the preoperative urinary loss of iodine varied considerably, the average daily loss was at the upper range of normal. A great increase followed total thyroidectomy. This gradually subsided, so that at the time of dismissal the urinary excretion of iodine was normal. The blood iodine rapidly decreased to about one-third normal.

CASE 4.—*Hypertensive Heart Disease With Congestive Heart Failure* (Table II). F. S., a white male, aged fifty-four years, entered the University Hospital on Apr. 3, 1934, for the management of hypertensive heart disease with recurrent severe decompensation. Hypertension had been present for many years. The severity of the congestive heart failure had increased in spite of medical management elsewhere. The physical findings were those of congestive heart failure. The blood pressure ranged between 180/98 and 202/108. The basal metabolic rate was minus 16, with the temperature 99°, the pulse 70, the respirations 16, and the weight 146 pounds in the basal state. *No iodine in any form was used or administered.*

Laboratory investigation revealed negative Wassermann and Kahn reactions. The blood picture was normal. Upon repeated urine examinations, only a trace of albumin was detected. The blood iodine was normal, Table II. During the preoperative period the daily urinary iodine ranged from 22 to 110, averaging 54 micrograms.

Total thyroidectomy was accomplished on May 2, 1934, using avertin (80 mg. per kilogram) supplemented by local anesthesia. The thyroid gland weighed 18 grams. There was an occasional small colloid nodule; otherwise the gland was normal. Analysis revealed an iodine content of 97 mg. per cent (dry basis), which is subnormal. For ninety-six hours after thyroidectomy there was a great increase in urinary excretion of iodine. This rose to 2.2 mg. and then gradually decreased.

TABLE II

HYPERTENSION WITH RECURRENT CONGESTIVE HEART FAILURE FOR MANY YEARS

(CASE 4)

DATE	24-HOUR URINE VOLUME (C.C.)	IODINE MICROGRAMS %	IODINE EXCRETED IN MG.	BLOOD IODINE MICROGRAMS %	B. M. R.
4/ 9/35	----	----	----		Minus 16
4/21/35	1980	1.1	0.022	10.2	
4/22/35	2420	2.0	0.048		
4/23/35	3220	----	----	8.5	
4/24/35	2970	3.7	0.110		
4/25/35	2440	2.1	0.051	10.1	
4/26/35	2700	1.8	0.049		
4/27/35	2000	2.7	0.054	11.2	
4/28/35	1240	2.6	0.032		
4/29/35	1830	3.8	0.069	10.1	
4/30/35	2000	2.6	0.052		Minus 16
5/ 1/35	1980	2.6	0.052		
5/ 2/35	----	----	----	7.6 (preoperative)	
		TOTAL THYROIDECTOMY, MAY 2, A.M.			
5/ 2/35	680	175.0	1.190	23.0 (2 hr. postoperative)	
				26.0 (4 hr. postoperative)	
				28.0 (6 hr. postoperative)	
				37.0 (9 hr. postoperative)	
5/ 3/35	420	270.0	1.150	28.0 (24 hr. postoperative)	
5/ 4/35	1320	170.0	2.240		
5/ 5/35	1190	170.0	2.023		
5/ 6/35	1190	----	----		
5/ 7/35	----	----	----	15.0	
5/ 8/35	640	41.0	0.260		
5/ 9/35	240	23.0	0.055		
5/10/35	300	24.0	0.072		
5/11/35*	440	13.0	0.057		
5/21/35	----	----	----		Minus 20
5/22/35	----	----	----	12.6	
6/ 8/35	----	----	----	6.9	

*The determinations of urinary iodine terminated on this day.

The average daily excretion of iodine during the postoperative eight days was 881 micrograms. Simultaneous with this increased urinary loss the blood iodine increased to 37 micrograms per cent, Table II, and then gradually decreased. It fell to 6.9 prior to dismissal from the hospital. The basal metabolic rate at this time was minus 20, with the temperature 97.8°, the pulse 44, the respirations 20, the weight 160 pounds, and the blood pressure 210/120 in the basal state. Throughout the postoperative course, the blood pressure fluctuated around 204/100. No immediate or remote complications were encountered.

Comment.—The preoperative average daily urinary excretion of iodine was within normal range. Immediately following total thy-

roidectomy the characteristic increase in the urinary loss of iodine ensued. This gradually subsided so that at the time of dismissal it had returned to normal.

CASE 5.—*Chronic Myelogenous Leucemia With Congestive Heart Failure* (Table III). A. D., a white male laborer, aged fifty-four years, entered the University

TABLE III

RECURRENT CONGESTIVE HEART FAILURE OF 8 MONTHS' DURATION (CASE 5)

DATE	24-HOUR URINE VOLUME (C.C.)	IODINE MICROGRAMS %	IODINE EXCRETED IN MG.	BLOOD IODINE MICROGRAMS %	B. M. R.
10/23/35	490	2.8	0.014		
10/24/35	1040	2.0	0.021		
10/25/35	1520	2.8	0.043		
10/26/35	1550	10.6	0.164		
10/27/35	1420	2.5	0.036		
10/28/35	1260	2.2	0.028	13.6	
10/29/35	1310	1.9	0.025		
10/30/35	1540	2.1	0.032		
10/31/35	1380	2.3	0.032		
11/ 1/35	1710	2.8	0.048		
11/ 2/35	1400	9.8	0.137		
11/ 3/35	730	2.3	0.017		
11/ 4/35	1160	2.6	0.030		
11/ 5/35	1480	2.5	0.037		
11/ 6/35	1360	4.4	0.060		
11/ 7/35	1280	3.7	0.050	7.9	Plus 41
11/ 8/35	1640	16.0	0.260	10.1	Plus 55
11/ 9/35	610	5.3	0.032	11.6	
11/10/35	1320	4.1	0.054		Plus 58
11/11/35	660	7.2	0.048		
11/12/35				7.4 (preoperative)	
		TOTAL THYROIDECTOMY, NOVEMBER 12, A.M.			
11/12/34	600	215.0	1.292	16.8 (4 hr. postoperative)	
				21.0 (7 hr. postoperative)	
11/13/35	920	104.0	0.960	15.0	
11/14/35	1120	53.0	0.590	(24 hr. postoperative)	
11/15/35	1130	20.0	0.230	9.3	
11/16/35	1250	7.1	0.089		
11/17/35	1060	5.6	0.059		Plus 34
11/18/35	980	5.4	0.053		
11/19/35	----	----	----	7.4	
11/20/35	770	5.2	0.040		
11/21/35	680	4.4	0.030		
11/22/35	1190	5.7	0.068		
11/23/35	1140	4.9	0.056		
11/24/35	1240	3.9	0.048		
11/25/35	1450	5.5	0.080		
11/26/35	----	----	----		Plus 18
11/27/35	800	4.5	0.036	6.3	
11/28/35	1780	5.2	0.093		Plus 20
11/29/35	1150	8.4	0.097		
11/30/35	----	----	----		Plus 16

Daily observations were continued until June 1, 1935. The urinary iodine remained within the normal range. The B. M. R. eventually fell to minus 13.

Hospital for the management of myelogenous leucemia with associated arteriosclerotic heart disease. About a year prior to admission he noticed a rapidly enlarging spleen. This was treated by intense x-ray therapy which resulted in a moderate reduction in its size. He was discharged from the hospital on Feb. 17, 1934. Shortly after his dismissal from the hospital he became aware of increasing dyspnea and edema of the feet and ankles, which became progressively worse.

He was readmitted to the University Hospital on Oct. 13, 1934, for further investigation. The physical findings were those of congestive heart failure. Laboratory examination was essentially negative save for the blood picture, which was that of chronic myelogenous leucemia. The basal metabolic rate fluctuated between plus 30 and plus 58 with the temperature 98.6°, the pulse 72, the respirations 17, the weight 145 pounds, and the blood pressure 106/56 in the basal state. *No iodine in any form was used or administered.*

The blood iodine ranged from 7.4 to 14.7 and averaged 10.6 micrograms per cent. The loss of iodine in the urine during the period of preoperative preparation ranged from 14 to 260 micrograms, and averaged 58 daily.

Total thyroidectomy was accomplished under a basal anesthesia of avertin with supplementary novocaine on Nov. 12, 1934. The gland removed was morphologically normal and weighed 10 grams. It was pale and soft. It contained 4.7 mg. of iodine. During the twenty-four hours subsequent to total thyroidectomy, the urinary iodine rose to 1.3 mg. The average daily urinary loss during the first eight days postoperative was 414 micrograms. This subsequently returned to normal. Associated with the immediate postoperative increase in the urinary iodine, there was a corresponding increase in the blood iodine, to 21 micrograms per cent. This subsequently fell as low as 4.5. Except for subcutaneous capillary hemorrhage during the first twenty-four hours after the total thyroidectomy, there were no complications.

Comment.—The effect of total thyroidectomy on the leucemic blood picture is to be reported elsewhere. The average daily preoperative excretion of iodine was normal. Following total thyroidectomy, the characteristic transitory increase in the urinary loss of iodine was noted. The urinary iodine gradually returned to a low normal range.

CASE 6.—*Chronic Myelogenous Leucemia With Congestive Heart Failure* (Fig. 3). S. R., a white male laborer, aged forty years, was admitted to the University Hospital on Jan. 18, 1935, for diagnosis. About fifteen years ago he noticed intermittent sharp pain in the left upper quadrant. Since that time he has experienced similar recurrent pain in this region. In June, 1933, a splenomegaly was discovered, for which splenectomy was performed elsewhere. Hodgkin's disease was suspected at that time. About a month after the splenectomy his white blood count was 50,000. There was an associated anemia. Bleeding from the gums occurred at intervals, and as a result his teeth had been extracted. About five weeks prior to his admission he became aware of dyspnea on exertion, swelling of the abdomen, and also edema of the feet and ankles. Physical examination revealed findings characteristic of congestive heart failure.

The hematologic picture was that of chronic myelogenous leucemia. The basal metabolic rate was plus 15 with the temperature 97.6°, the pulse 77, the respirations 15, the blood pressure 168/108, and the weight 169 pounds in the basal state. Because of the congestive heart failure, total thyroidectomy was advised and accomplished on Feb. 26, 1935, using a basal anesthesia of avertin supplemented by

novocaine locally. The gland removed weighed 24 grams. It revealed no evidence of abnormality. Except for moderate controllable subcutaneous oozing from the wound during the first twenty-four hours following the total thyroidectomy, there were no complications.

During the preoperative period the urinary iodine varied from 17 to 153, averaging 91 micrograms daily. During the twenty-four hours subsequent to total thyroidectomy it increased to 2.0 mg. The average daily urinary excretion for the first eight postoperative days was 385 micrograms. It gradually decreased, so that at the time of dismissal it was at the lower range of normal. The average daily postoperative loss of iodine in the urine during an eleven-day period was 262 micrograms.

At dismissal, March 17, 1935, the basal metabolic rate was minus 5, with the temperature 97.4°, the pulse 74, the respirations 15, the weight 150 pounds, and the blood pressure 140/90 in the basal state.

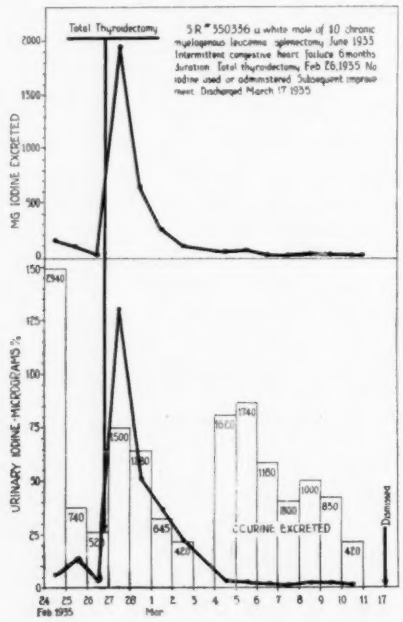
Total Thyroidectomy
SR 350336 a white male of 10 chronic myelogenous leucemia splenectomy June 1933 Intermittent congestive heart failure 6 months Sunstroke Total thyroidectomy Feb 26.1935 No iodine used or administered Subsequent improvement Discharged March 17 1935
MG IODINE EXCRETED
URINARY IODINE-MICROGRAMS %
CC URINE EXCRETED
Dismissed
Feb 1935
Mar

Fig. 3.—The urinary excretion of iodine following total thyroidectomy.

Comment.—During the preoperative period the average daily urinary excretion of iodine was increased over normal. Immediately following total thyroidectomy there was an even greater increase. This gradually decreased to the lower range of normal.

DISCUSSION

The duration of postoperative hospitalization of the six patients varied, depending upon the clinical improvement and the extent of subsequent investigation. The results of the first eight postoperative days are presented for comparison in Table IV. The average daily loss of iodine during the entire postoperative periods is noted in the individual case reports.

Table IV summarizes the average daily preoperative loss of iodine. Two of the patients fall within the normal range. Two are at the upper limit and two are definitely high. The preoperative grand average is 0.094 mg. This is higher than normal.[15] The reason for the increased blood iodine,[10] as well as the greater urinary loss, is not wholly clear. It may be a metabolic manifestation of cardiovascular disease. Perhaps secondary demands are made by the primary disease upon the thyroid mechanism as related to oxidation. Conceivably the nonthyroid iodine metabolism may be involved. Further investigation is necessary.

TABLE IV

LOSS OF IODINE IN THE URINE FOLLOWING TOTAL THYROIDECTOMY

PATIENT NO.	DIAGNOSIS	PREOPERATIVE DAILY IODINE EXCRETION		POSTOPERATIVE DAILY IODINE EXCRETION	
		RANGE	AVERAGE	RANGE	AVERAGE
		MG.	MG.	MG.	MG.
1	Hypertensive heart disease	0.066 to 0.408	0.210	2.635 to 0.043	0.711
2	Hypertension	0.028 to 0.176	0.077	2.470 to 0.031	0.547
3	Hypertension	0.010 to 0.130	0.075	1.630 to 0.036	0.672
4	Hypertensive heart disease	0.022 to 0.110	0.054	2.240 to 0.055	0.881
5	Chronic myelogenous leucemia with congestive heart failure	0.014 to 0.260	0.058	1.290 to 0.053	0.414
6	Chronic myelogenous leucemia with congestive heart failure	0.017 to 0.153	0.091	1.950 to 0.011	0.385
		Grand average preoperative	—— 0.094	Grand average for first eight days postoperative	—— 0.601

Considerable variability in the postoperative urinary excretion of iodine was observed. The average daily loss during the first eight postoperative days ranged from 2.635 mg. down to 0.011 mg. The grand average was 0.601 mg. It is obvious from these data that *immediately following total thyroidectomy for cardiovascular disease there ensues a great increase in the urinary loss of iodine.*

Cattell[22] determined the urinary excretion of iodine during iodine medication in patients with exophthalmic goiter. He observed a postoperative *decrease* in iodine elimination. This was most evident during the first three postoperative days. The increased postoperative loss which we report is comparable to that observed following partial thyroidectomy by Curtis and Phillips.[11]

Thyroidectomy in man, either partial, subtotal, or total, is thus followed by a transient but definite increase in the urinary loss of iodine. This persists for a varying period and then subsequently returns to normal. Up to 5 mg. of iodine may be thus rapidly lost. An adequate explanation for this is not at present possible. Manipu-

lation and trauma to the thyroid gland possibly account for a part of the immediate increase. These factors, however, do not account for its persistence. Too, we have observed[16] that following non-thyroid operations on remote parts, such as astragalectomy, herniorrhaphy, and thoracoplasty, there is also an immediate postoperative increase in the urinary loss of iodine which persists for a varying period. It is possible that such procedures stimulate the thyroid gland to liberate increased amounts of iodine-containing substances, hence the postoperative increase in the blood iodine as well as the increased urinary loss. Both, however, occur following total thyroidectomy. After due consideration of the data available, a more comprehensive hypothesis is that the increased loss of iodine in the urine is a result of depletion of the extrathyroid tissues.

CONCLUSION

Following total thyroidectomy for cardiovascular disease, there ensues a great increase in the urinary loss of iodine. This is variably transient, usually persisting for about forty-eight hours. The daily iodine excretion subsequently returns to a lowered normal range. These data present added evidence that a part of this increased postoperative loss of iodine originates from the extrathyroid tissues. It is possible that the thyroid gland exerts an as yet unrecognized effect upon the tissue iodine.

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VENOUS STASIS ACCELERATES BONE REPAIR

HERMAN E. PEARSE, JR., M.D., AND JOHN J. MORTON, M.D.,
ROCHESTER, N. Y.

(From the Department of Surgery, The University of Rochester School of Medicine and Dentistry)

IN 1930 we[1] reported clinical and experimental observations leading to the conclusion that bone repair was accelerated by venous stasis. At that time it was pointed out that stasis hyperemia had been used clinically since the time of Ambroise Paré to promote the formation of callus in fractures. The statement of Nicoladoni that "an artificially produced and permanently maintained hyperemia will exercise a powerful stimulus on the tissues and tissue elements which participate in callus formation" was quoted. Others advocating venous stasis to increase deficient callus formation and to stimulate bone regeneration were mentioned. Our own experience in clinical cases was given.

References were also cited to show that many observers had noted the correlation between venous stasis and the overgrowth of bone in pathologic states. Conditions such as meningioma, long-standing leg ulcers, arteriovenous aneurysms, hemangiectasis, varicose veins, and congestive cardiac failure, have been considered responsible for increases in the length and thickness of bone. Harbin[2] has observed this effect in a patient with nevus and congenitally enlarged veins, and recently Harris and McDonald[3] have reported a similar change following extensive thrombophlebitis of the femoral and iliac veins.

Finally, twelve experiments in dogs were reported in which both fibulas were divided and the popliteal vein of one side was ligated. In eleven of these twelve experiments the accelerated healing due to venous stasis was manifested by earlier formation of callus and earlier union.

From these data we concluded that venous stasis caused stimulation of bone growth. We reemphasized this in a subsequent paper.[4]

Observations were made later by McMaster and Roome[5] who repeated our experiments and confirmed our results. They sectioned the dog's fibula, compared healing with and without vein ligation, and concluded that "experimental venous stasis in dogs hastened bone repair." In a second paper Roome and McMaster[6] demonstrated that heterotopic bone is also increased by venous stasis. They made autotransplants of the mucosa of the urinary bladder into the muscles of the dog's hind legs. On one side the veins were occluded, and here a greater amount of bone was formed in the transplant. By this ingenious experiment the authors contributed evidence different from any previously offered on the subject.

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From the foregoing statements one might consider as a fact that bone growth was stimulated by venous stasis. It was so considered until Key and Walton[7] threw doubt upon it by failing to produce the effect in dogs. They admit that they have obtained healing in clinical cases of delayed union of fractures treated by passive hyperemia, so that apparently only the experimental findings are questioned.

Key and Walton tried our experiment on the fibula in six dogs which, when killed for study in ten weeks, showed only one instance of firmer union on the ligated side. They judged this to be due to the "unhappy choice of the site of bone defect." This is rather an amazing statement, for the fibula has been used by Harvey and his coworkers,[8] McMaster and Roome,[6] Zollinger,[9] Sweeney and Laurens,[10] and others for experiments on bone repair. Moreover, we selected it only after careful dissections had shown that it had the best relation of venous return to bone defect for a test of our question. Key and Walton, however, felt that the ulna was a preferable location. They operated upon twenty-four dogs, resecting approximately 0.5 cm. of bone and tying all the veins in sight, so that the animals' legs become edematous for two weeks or more. No difference in healing was observed between the ligated and control sides and on the strength of this, the authors challenged our findings.

When we read their paper, we felt that they had condemned our results *without adequately repeating our experiments.* They discarded the fibula after six experiments, the results of which were judged, as far as one can tell, from sacrifice of the animal at the arbitrary time of ten weeks, without taking serial roentgenograms to observe the rate of healing. In their work on the ulna, conditions prevailed that were absent from our experiments, for they ligated "all the large veins which could be identified in the region of the elbow" (both superficial and deep), causing persistent swelling and edema. This indicates circulatory failure and must have been associated with impaired function of the extremity; therefore a comparison was made between conditions resulting in circulatory and functional disability and those in which these factors were absent. This did not look right, but as Key and Walton were attacking the validity of our results on the basis of these experiments, we felt obliged to repeat them.

RESECTION OF THE ULNA

We originally intended to do a series of ulnar resections, but after operating upon seven dogs we were convinced that it was a poor place for the experiment. For not only was there postoperative swelling, edema, and disability from the indiscriminate tying of veins, but also there was *excessive bleeding* at the time the bone was sectioned. The latter was sometimes venous, sometimes arterial, and came from deep within the wound. This demanded an explanation, for it violated the premise that the only alteration of the circulation was that produced

intentionally to create the conditions of the experiment. Consequently, the blood supply of the dog's foreleg was studied by dissection. It was found that the volar interosseous artery and vein (or veins) occupied most of the space between the radius and the ulna (Fig. 1). These vessels in the dog are as large as any others in the foreleg. With all the muscles stripped off the leg, and the bone and vessels in view, it was sometimes impossible to do a subperiosteal resection of the ulna without injuring them. In fact, occasionally one could not insert a knife blade between bone and artery without damage to the latter. Imagine the uncertainty of trying to avoid these vessels while working through a surgical incision!

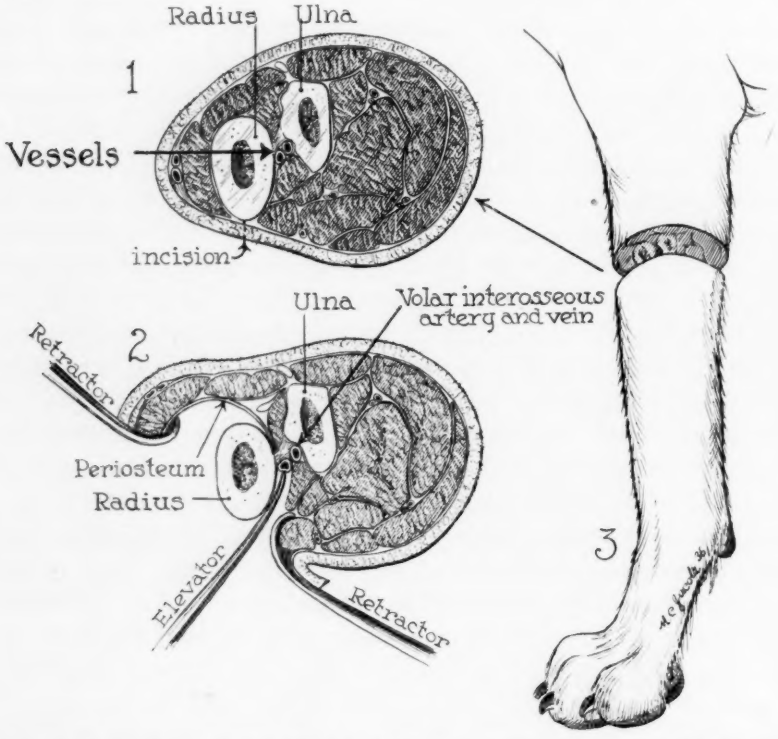

Fig. 1.—The anatomy of the dog's foreleg. *1*, a cross-section illustrating the intimate relation of the volar interosseous vessels to the bone; *2*, a schematic drawing to show how these vessels may be injured in the operation of Key and Walton.

We found, as did Key and Walton,[7] that there was no increase in the rate of bone repair on the side having the veins tied. But we considered the results meaningless in view of the uncontrolled factors existing in the experiment.

OTHER LOCATIONS FOR BONE RESECTION

As Key and Walton did not like our use of the fibula and we felt even more strongly about their selection of the ulna, it appeared desirable to try some other location for the experiment.

We tried removing a segment of the radius, but here, as with the ulna, damage to the interosseous vessels occurred; therefore the foreleg was eliminated as a suitable site for trial. The next attempt was to create bilateral burr holes in the skull, but here the arrangement of the diploic veins made it impossible to obtain unilateral venous stasis. Next, bilateral rib resections were tried and the intercostal veins were ligated and divided on one side. A preliminary series of four experiments was done in this manner. In all it was found that the small intercostal veins regenerated rapidly by collaterals, thus preventing adequate venous hyperemia. Then defects in the tibia were tried, first by creating a U-shaped defect in the crest, and later by burr holes just below the tubercle. It was found that the defects in the tibial crest smoothed out

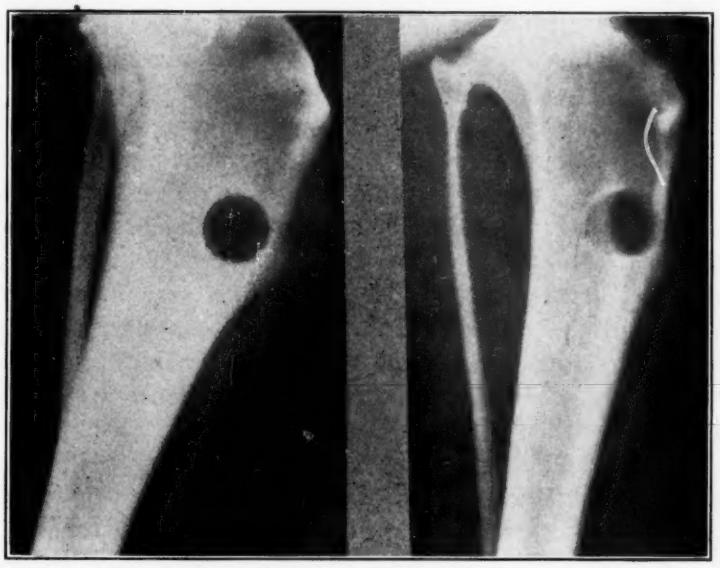

Fig. 2.—When a burr hole in the tibia is used to study bone repair, a false impression of healing of the defect is given by slight rotation of the leg in taking the x-ray (right).

in healing so that no sharp end point could be relied upon; hence they were discarded. Since the burr holes through the tibia just below the tubercle appeared more satisfactory, nine dogs were operated upon, burr holes being made in both sides and the popliteal vein ligated in one leg. In view of the collateral anastomoses about the knee joint one might question the amount of venous stasis produced, but this was not the most serious objection, for it was found that unless the direction in which the roentgenogram was taken corresponded exactly with that of the burr hole, overlapping of the edges occurred, giving the impression of greater calcification than actually existed (Fig. 2). This made one distrust the results, and even though some of the animals showed accelerated bone repair on the side of the venous stasis, the findings were considered inconclusive.

To satisfy our requirements it was necessary to do the bone resection in such a way that postoperative splinting was eliminated, functional disability was minimized, and damage to the circulation avoided. In addition, the venous stasis had to be adequate in the region of the bone defect, yet cause a minimum change in the remainder of the circulation. We had originally chosen the fibula as best meeting these requirements, and after trying other locations, we were convinced that it was the most desirable location for the purpose.

RESECTION OF FIBULA

It was decided to repeat our original experiments; eighteen dogs were operated upon, resecting between 3 and 4 mm. of both fibulas in the upper third and ligating the popliteal vein on the right. This technic has been described,[1] but it might be well to amplify some details. The bone resection is easier if the hind legs are placed on round sandbags supporting the upper calf, and the ankle is pulled to the edge of the table by a strap. This steadies the legs and flattens out the muscles. Bleeding is avoided by approaching the fibula through intermuscular septa, but when the bone is reached, muscle is found to attach to the periosteum. The fibers, however, run laterally from each side so that, approaching from the back, it is usually possible to cut the periosteum for an inch without dividing any muscle. The placing of a small mastoid retractor at this stage gives good exposure, after which the periosteum may be freed. This requires care, for the periosteum is thin, but with delicate instruments and technic its separation is not particularly difficult. The best tools are a slightly curved, thin, blunt elevator about 5 mm. wide, which is often used in submucous resection, or a dental elevator, which is usually a little narrower. A right-angle dental elevator is sometimes useful to free the undersurface of the bone. After separating the periosteum, it is held down in order that the bone may be lifted and cut with a small Hibbs spinous process cutter.

Attention is given the details of bone resection, for it is our feeling that most failures can be traced to improper technic resulting in loss of continuity of the periosteum, thus allowing muscle to interpose between the fragments. Another possible error is to mistake the lesser saphenous vein for the smaller, more concealed popliteal at the time of vein ligation. If this is done, no venous stasis results in the region of bone resection.

The technic of our experiments on the fibula has become as nearly standardized as any surgical operation could be. Thus we may confidently expect that if a result is obtained, it will be due to the conditions of the experiment and not to chance. We found that of the 18 dogs having bilateral resection of the fibula and unilateral popliteal vein ligation, 14 showed accelerated healing on the side having the vein tied (Fig. 3). In 2 animals there was no difference in the rate of repair,

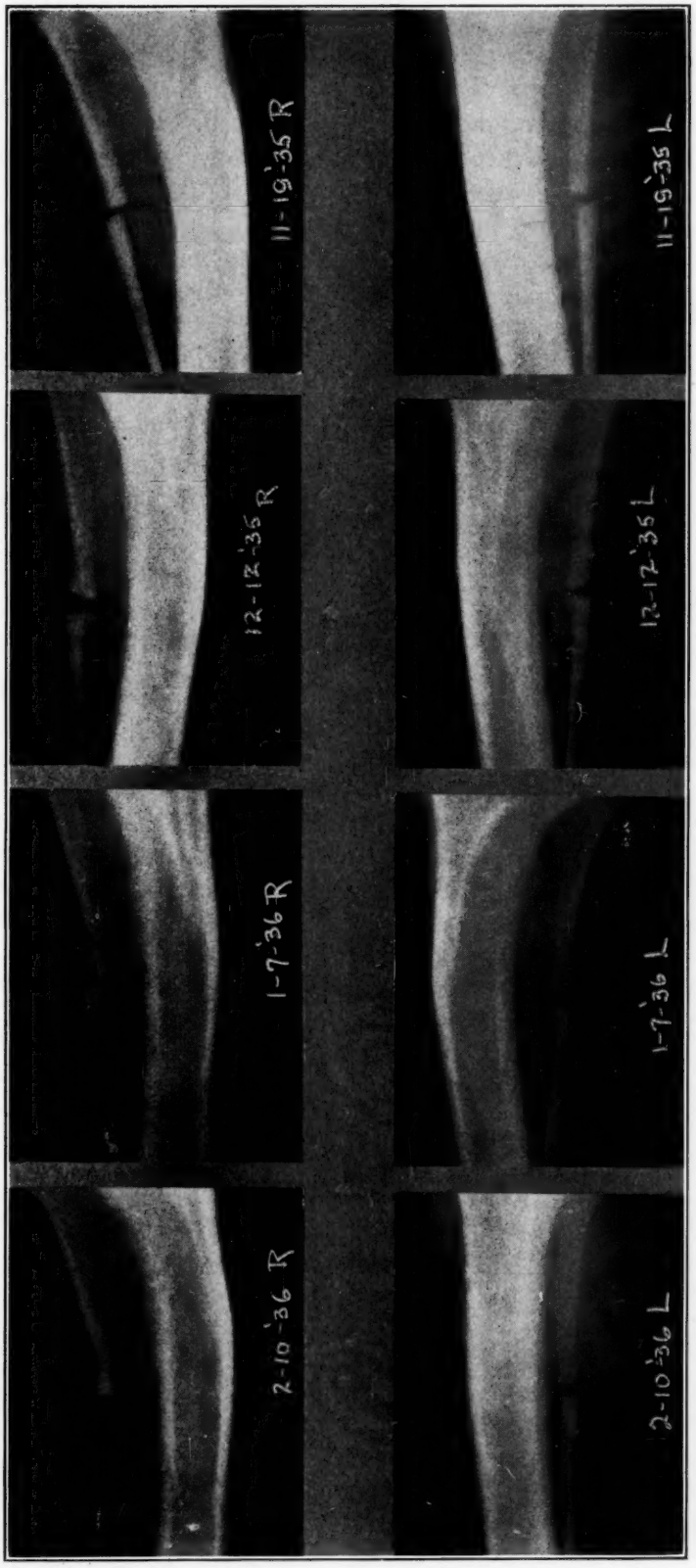

Fig. 3.—The right side (shown to the left in the illustration) reveals the accelerated healing with venous stasis in comparison to the normal repair on the left.

and 2 died of distemper before the experiment was completed. Combining these results with those already published, one finds that of 30 experiments, 25 showed increased bone growth with venous stasis, 3 had no change, and 2 were terminated by the death of the animals. Eliminating the latter from calculation gives 25 out of 28, or 90 per cent of the animals, which showed accelerated bone repair with venous hyperemia. The increase in rate of healing was considered moderate or extreme in 15 and only slight in the remaining 10. These latter were all in our recent series and rather surprised us, for we had observed no *slight effects* in our original experiments. The apparent explanation was found, however, in the fact that 8 of the 10 were young dogs. In young animals bone defects heal in about five weeks rather than the nine or ten weeks required by the mature adult. It was felt that the speed of this reparative reaction was such that it could not be increased much beyond the normal rate of repair; hence the effect of the venous stasis was not as apparent as in the older animals.

SUMMARY

In previous publications we showed that venous stasis had long been used to accelerate the healing of fractures, an observation which we were able to confirm. Moreover, many writers had noted the overgrowth of bone when venous hyperemia was caused by pathologic processes. In addition, 28 experiments on dogs' fibulas have revealed increased healing in 25 (90 per cent) of the animals, on the side having venous congestion produced by ligation of the popliteal vein. This observation has been confirmed by McMaster and Roome[5] who, in addition, showed that heterotopic transplants of bone grew more rapidly with venous hyperemia. Although this fact has been questioned by Key and Walton,[7] we feel that the weight of evidence is sufficient to warrant reiteration of our contention that venous stasis stimulates bone growth.

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SYNOVIOMA

Report of Fifteen Cases With Review of Literature

Bradley L. Coley, M.D., and John C. Pierson, M.D., New York
(From Bone Tumor Department of Memorial Hospital and the Hospital for the Ruptured and Crippled)

UNTIL a decade ago, little attention had been paid to a form of malignant tumor occurring in or about joints, characterized by a distinctive histologic appearance, a tendency to recur after excision and often to metastasize to the lungs. Their origin from synovial membrane is now established. They may be found, therefore, within the joint cavity, but may also arise from bursae, or from pouches or prolongations of the joint. They may also involve connective tissue, tendon sheaths, and lymphatics. They may give rise to symptoms which may simulate many of the more common conditions arising within the joints.

HISTORICAL

One of the first cases of primary synovial tumor was reported in 1865 by Langenbeck.[10] In 1894, Hardie and Salter[6] reported one case and mentioned another. C. B. Lockwood[12] and G. R. Turner[16] each reported a case in 1902. In 1910, Lejars, and Rubens Duval[11] published a case report. Then Faccini, cited by Smith,[15] reviewed all cases to 1923. Four years later Lawrence Smith[15] added three cases, introducing the term "synovioma," which, while it departs from the custom of designating a tumor according to its embryologic origin, has several advantages. As Smith has pointed out, the term obviously indicates the tumor's origin, yet "offers a loophole of escape when the exact tissue of origin is debatable." It is one that easily lends itself to classification in any published index, and follows the precedent for nomenclature in such tumors as hypernephroma and meningioma.

Talbot, cited by Faulkner,[5] added three cases in 1928, his discussion being limited to primary synovial membrane tumors containing giant cells. In 1931, Razemon and Bizard[14] reviewed the literature for all primary tumors of the articulations and found 74 cases. Of these, 29 were malignant fibro spindle cell sarcoma. Many of these tumors were called "Tumeurs a cellules geantes," these being subdivided into the diffuse and circumscribed. Although one cannot be certain these might be classed as synoviomas. There are eight well-defined cases included in this report that are probably of synovial origin; of these, six were in the knee; five recurred after excision requiring a second

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wide excision or amputation; three patients died of pulmonary metastases within one year after the first symptoms were noticed. L. C. Wagner[17] also reported two cases in 1931. One of these, a synovioma of the right knee, recurred after local excision and finally came to amputation. Postoperative treatment included irradiation and a thorough course of Coley's toxins. The patient remained well for ten years and is one of the few known to have survived a five-year period. He died, however, of pulmonary metastases in October, 1935. The second patient is well three years following local excision at the ankle. Again the literature was briefly reviewed by Faulkner[5] in 1931 and two cases were added. Both of these occurred in the knee, were excised locally, and were given high voltage x-ray therapy with no evidence of recurrence or metastasis six years later. In 1933, Leila Charlton Knox[8] added three cases. Two of these patients died of pulmonary metastases four and six years, respectively, following amputation. In one of these cases the chest metastases were treated with high voltage x-rays, but with no improvement. In April, 1934, W. B. Coley[3] presented before the New York Surgical Society a case of synovioma of the knee joint treated by excision. Following recurrence, it was again excised with removal of the patella, and a course of Coley's toxins was given together with high voltage x-ray therapy. The patient remained well three years. A case of "Synovialoma" (Histiocytoma) was reported by L. La Ferla and G. Demelas[9] that same year. In 1935, Hodgson and Bishop[7] reported an interesting case of synovioma of the knee, the patient giving a history of trauma eight months before the discovery of the tumor. High-voltage x-rays and Coley's toxins were tried without benefit. Hydrarthrosis and lymph stasis developed, followed by inguinal adenopathy. Finally, metastases appeared in the skin of the thigh as little shotlike masses which later broke down, draining serous fluid. An excised skin nodule showed the same structure as did one of the inguinal nodes. Death occurred seven months after the onset of the disease.

Since 1900, 24 cases of primary synovial membrane tumors have been observed at the Memorial Hospital. Some of these were merely sections submitted for diagnosis, and because of insufficient follow-up data these are not included in this report. There are, however, 15 cases that have been carefully followed, the detailed reports of which are here given.

CASE 1.—H. M., a forty-five-year-old Austrian cabinet maker, was admitted to the Memorial Hospital, service of Dr. James Duffy, on Dec. 1, 1934. He complained of a swelling on the radial aspect of the left index finger of seven months' duration. There was no particular trauma, although he continually injured his finger while pursuing his trade. Three months after the appearance of the tumor, it was excised, only to recur. Examination disclosed a firm, movable nodule 7 mm. in diameter on the radial side of the first interphalangeal joint. There was moderate tenderness.

A few smaller nodules were found on the dorsum of the finger. Extension was limited to 150 degrees. There was no adenopathy. X-ray films showed a soft part tumor of the left index finger, with no bone involvement.

Pathologic Report.—Of submitted slide, synovioma (Stewart).

Treatment.—Prophylactic irradiation to the left index finger, using a dosage of 800 r. to each of two portals. This was given within a period of eighteen days. *Factors:* 198 K.V. S.T.D. 50 cm. Field: 5.2 × 5.2 cm.

Course.—Has had 1,600 r. to each of two portals, but tumor continues to grow. Chest film negative for metastases. Patient advised to have amputation, to which he consents. (Jan. 15, 1936.)

CASE 2.—J. C., a nine-month-old male infant, was admitted to the Memorial Hospital in April, 1931, service of Dr. F. E. Adair. When the child was two months old, the parents had noticed a tumor of the left knee mesial to the patella. At that time the tumor was excised, but recurred within one month. Examination revealed a tumor of the left knee extending 4 cm. above and below the patella. There was no bone involvement.

Operation.—Wide excision by Dr. Adair on April 22, 1931. The joint became infected and erysipelas developed, following which the patient made a satisfactory recovery.

Pathologic Report.—Mesothelioma arising in the synovial structures malignant and capable of metastases. (Stewart.)

Irradiation.—Four months postoperatively irradiation was begun, giving 595 r. to each of two portals for a total of 1,195 r. in six months. *Factors:* 198 K.V. S.T.D. 50 cm. Field: 10 × 10 cm.

Course.—Three years and six months later the chest film was negative for metastasis, and there was no evidence of recurrence. Left leg 2 cm. shorter than the right. Patient was perfectly well and gaining weight.

CASE 3.—V. C., a twenty-four-year-old American student, was admitted to the Memorial Hospital April 13, 1931, service of Dr. Adair. Six months prior to entry he noticed a pain in the heel of the right foot. Ten months later he noticed a tumor in the intermalleolar fossa extending down to the heel. A local excision was done, with prompt recurrence of the tumor. Examination disclosed a scar on the right lower leg 8.0 cm. in length, extending from the side of the heel up to the malleolus. There was no adenopathy. X-ray films showed slight periostitis of the shaft of the fifth metatarsal. A chest film was negative for metastasis; however, on March 14, 1932, nodules interpreted as advanced pulmonary metastases were seen throughout both lung fields.

Pathologic Report.—Of submitted slide, synovioma (Stewart).

Irradiation.—Given 2,520 r. to each of two portals over a period of one year. Also 1,600 r. to chest. *Factors:* Foot: 140 K.V. S.T.D. 38 cm. Chest: 200 K.V. S.T.D. 70 cm.

Course.—Died April, 1932, of pulmonary metastases, two years and six months after first symptom was noticed.

CASE 4.—L. B., a thirty-five-year-old Canadian clergyman, was admitted to the Memorial Hospital January 15, 1934, service of Dr. William L. Watson, complaining of swelling on the plantar surface of the right foot of three years' duration. The swelling had progressed so that in one year it had extended to the dorsum of the foot. It was aspirated in 1932 and again in 1934. Patient experienced severe pain on walking, even when no shoe was worn. Examination revealed a soft tumor, which could be somewhat reduced by pressure, located on the plantar surface of the right foot and extending to the dorsum. There was no adenopathy. X-ray films showed no bone involvement.

Pathologic Report.—Synovioma, capable of metastasis.

Treatment.—On January 15, 1933, given 500 r. × 2. Patient then left the hospital and returned in two weeks, the pain being greatly relieved. From April 19 to 26, 1934, he was given 600 r. × 2. *Factors:* 140 K.V. S.T.D. 30 cm. On December 6, 1934, there was slight improvement, but the lesion had increased in size and weight-bearing was painful. Amputation was done at the upper third of the leg. The patient was fitted with an artificial limb and was walking within one month after entrance to the hospital.

Course.—Although the patient is now symptom-free, x-ray films of the chest in March, 1936, showed metastatic infiltration of both lung fields.

CASE 5.—M. S., a twenty-two-year-old American girl, was admitted to the Memorial Hospital September 15, 1933, service of Dr. Adair. Seven years prior to entry she suffered a slight trauma to the dorsum of the left hand, following which a lump the size of a bean appeared. There was no increase in size until fourteen months before entry, when it grew to the size of a hen's egg. Local excision was done twelve months before admission. Examination revealed a hard, fixed tumor on the dorsum of the left hand. There was no tenderness, and no sensory or motor involvement. One year after local excision, two discrete nodular shadows were seen, one just above the right diaphragm, the other on the third interspace. One month later, the patient had a pleural effusion. On Oct. 19, 1933, amputation was done 10 cm. above the wrist.

Pathologic Report.—Malignant synovioma or endothelioma.

Course.—Died January, 1935, of pulmonary metastases. Duration of symptoms—four years.

CASE 6.—M. T., a forty-seven-year-old Russian male, was admitted to the Memorial Hospital January 13, 1934, service of Dr. Adair, complaining of painful swelling of the left knee. Two years prior to entry he suffered severe trauma to the knee which soon became swollen and inflamed. Within a week this subsided and he resumed work. Four months after injury he noticed pain and swelling in the joint. Operation was performed, followed by two courses of irradiation of ten treatments each, extending over a period of three months. The patient was well for a year and a half, when he noticed pain on the inner aspect of the knee joint. The leg was placed in a cast for eight weeks, but the pain became more severe. More x-ray treatment was given, without improvement. On examination the knee was tender, shiny, epilated. It was enlarged and irregular in contour, the swelling being hard and confined to the anteromedial aspect of the knee joint. Motion was limited to about five degrees. X-ray films showed marked porosity of the bones of the left knee. There was no tumor of the bone or soft parts. The chest showed metastases. Amputation was done for pain, and the stump was revised twenty-two days later.

Pathologic Report.—A firm, yellow, edematous specimen with flecks of deposited calcium. No gross bone. A tendency to break down into villous cysts. Microscopic diagnosis: malignant synovioma.

Irradiation.—Preoperatively 72,000 r. × 4 to knee. One hundred eighty K.V. S.T.D. 40 cm. At Memorial Hospital he was given two cycles 750 r. × 3. *Factors:* 198 K.V. 50 cm. Fields: 15.6 × 7.8 cm. Total irradiation to knee 9,450 r. × 3. To chest 1,600 r. × 8. Patient died December, 1934, of pulmonary metastases. Duration of symptoms—three years.

CASE 7.—F. G., a thirty-five-year-old Jewish housewife, was admitted to the Memorial Hospital Nov. 1, 1934, service of Dr. Bradley Coley. Eight years before entry she suffered slight trauma to the right knee associated with mild pain. This was accompanied by slight swelling, then disappearance of the pain. One year before admission lamp treatments were given for the swelling. This was followed by an increase in size of the knee and continuous pain. Examination showed the lateral

aspect of the right thigh near the joint to be somewhat swollen, with a tumor measuring 6.0 by 5.0 cm. There was no adenopathy. X-ray films showed a tumor of the soft parts just above the external condyle. There was no bone involvement.

Operation.—In November, 1934, local excision was done and a tumor communicating with the knee joint was removed.

Pathologic Report.—Synovioma capable of metastasis.

Irradiation.—One week postoperatively began with a dosage of 200 r. daily from Nov. 27, 1934, to Jan. 8, 1935, for a total of 2,400 r. × 3. *Factors:* 198 K.V. S.T.D. 63 cm. Field: 8 cm.

Course.—Patient was perfectly well June 22, 1936. Chest film negative for metastasis. Good function of the knee joint.

CASE 8.—N. C., a twelve-year-old American schoolgirl, was first seen by Dr. Schuyler Pulford in September, 1932. One year prior to observation she noticed a small lump over the left knee, which gradually developed into a painful mass the size of an ordinary lemon. There was no history of injury. X-ray films showed a pressure atrophy of the fibula.

Operation.—A local excision was done in September, 1932, by Dr. Gustav Wilson. At operation a tumor of grayish white soft tissue resembling brain substance was encountered. Following biopsy and exploration, a complete course of x-ray therapy was given, followed by amputation.

Pathologic Report.—Synovioma of low-grade malignancy and capable of metastasis. (L. Smith.)

Course.—Patient is wearing an artificial leg and is perfectly well six years after operation.

CASE 9.—I. S., a sixty-four-year-old white Russian locksmith, was admitted to the Memorial Hospital June 22, 1932, service of Dr. Adair, complaining of a tumor of the right foot of five months' duration. He did not see a physician until one week prior to entry, when he was referred to the Hospital for the Ruptured and Crippled. Examination disclosed a swelling on the inner surface of the foot about the internal malleolus. The only tenderness was on the plantar surface. X-ray films showed no evidence of bone tumor formation. Aspiration biopsy was attempted without success.

Operation.—Local excision was done Aug. 4, 1932.

Pathologic Report.—Spindle cell sarcoma suggestive of bursal or synovial origin. (Despite the report of no radiation, it looks like a treated case. There are abortive cell divisions, infarction, endarteritis, and sclerosis.) Process does not look highly malignant and looks as if it might sclerose with radiation.

Irradiation.—Given 800 r. × 2 in two days. *Factors:* 198 K.V. 0.5 mm. Cu S.T.D. 50 cm. Field: 8.0 × 8.0 cm.

Course.—Leg amputated below the knee on Sept. 14, 1932. Slides of this specimen showed the tumor to be a synovioma. Course was uneventful until June, 1934, when the stump began to show changes which appeared to be secondary to arteriosclerosis. In December, 1934, a midthigh amputation was done for arteriosclerotic disease. No tumor was found in this specimen. Films of the chest taken at this time were negative for metastases. The patient was last seen in January, 1936. There was a low grade inflammation in the stump which requires dressings. No evidence of pulmonary metastasis.

CASE 10.—M. P., a twenty-seven-year-old Jewish accountant, was admitted to the Memorial Hospital Sept. 4, 1934, service of Dr. George Pack. Nine months before admission the patient suffered an injury to the right palm with lacerations. The pain of the injury persisted until four months before admission, although baking and massage were used to alleviate it. The swelling that attended this injury persisted and increased until a local excision was done at another hospital three months prior

to admission. One week before admission a second excision was done, and a cystic, well-circumscribed tumor was removed. Examination revealed a healed, transverse incision across the palm, measuring about 3 by 3.5 cm. This traversed a soft, firm tumor mass. The fingers were semiflexed and forced extension caused severe pain.

Pathologic Report.—An aspiration biopsy was negative. A submitted slide from the second operation was reviewed by Dr. Ewing and found to be papillary endothelioma of tendon sheath or bursal origin. Grade 11 R.R. (synovioma).

Treatment.—Given 2,500 r. × 2 within ten days. *Factors:* 198 K.V. S.T.D. 50 cm. Field: 7.8 × 7.8 cm.

Course.—Tumor is now one-fifth its original size and the patient has good function of fingers. Chest films were negative for metastases Jan. 15, 1936.

CASE 11.—A. H., a sixteen-year-old Jewish schoolgirl, was admitted to the Hospital for the Ruptured and Crippled in November, 1933, service of Dr. William B. Coley. She complained of pain in the left knee of six months' duration. There was no associated trauma. Examination disclosed a freely movable, firm mass, the size of a lima bean, on the medial aspect of the knee.

Operation.—A local excision was done in November, 1933. In February, 1934, there was a recurrence. The patient was again operated upon, a wide excision of the tumor with excision of the patella being done.

Pathologic Report.—Fibrosarcoma of synovial membrane (synovioma).

Course.—In March, 1934, the patient received irradiation with the 4 gram radium element pack at 6 cm., the dosage being 22,000 mg. hr. mesially, and 16,000 mg. hr. laterally (March 25 to 31). When last seen in April, 1936, she was perfectly well, had good function of the joint, and walked without a limp. Chest films were negative for metastases.

CASE 12.—M. D., a forty-five-year-old American housewife, was first seen by Dr. Fred O. Coe on Jan. 8, 1930. One month prior to observation, she complained of a painful swelling over the ball of the left great toe. This was regarded as a bursitis, and the head of the second metatarsal was resected. Two months after operation, several small nodules appeared close to the scar. The patient was given x-ray therapy without effect, and definite recurrence was found in August, 1932, twenty-one months after operation.

Operation.—A local excision was done in March, 1933, and again in August, 1933. The patient was given two x-ray treatments amounting to a full erythema dose.

Pathologic Report.—Synovioma.

Irradiation.—In January, 1934, a small subcutaneous mass was palpable, and within three days 1,200 r. × 2 were given. Patient received 4,500 r. × 2 within a period of nine months. *Factors:* 220 K.V. Filter: 1.2 mm. Cu Field: 7.0 × 7.0 cm.

Course.—When seen in August, 1935, she was perfectly well. Chest films were negative for metastases. Fairly good function of foot.

CASE 13.—M. G., a forty-five-year-old white Hebrew, was admitted to the Lincoln Hospital on July 3, 1935, service of Dr. S. Epstein, complaining of a tumor mass of the left knee. In September, 1932, he noticed a painless lump in the region of the left patella, which slowly grew to the size of a small orange. It was thought to be a lipoma and was excised as such in July, 1933. No pathologic examination was made of this specimen. In December, 1933 (five months after operation), there was a recurrence.

Operation.—In March, 1934, an extensive excision of the tumor mass with a pedicle graft to cover the exposed patella was done. In May, 1935, fourteen months later, there was another recurrence, and the tumor mass was again excised.

Pathologic Report.—Synovioma (Stewart).

Course.—When last seen in June, 1936, the patient was found to have another recurrence; amputation advised.

CASE 14.—J. M., a twenty-nine-year-old Jewish housewife, was admitted to the Memorial Hospital April 1, 1936, service of Dr. W. B. Coley. Nine years prior to entry she noticed pain in the right popliteal space while horseback riding. There was no history of trauma. Two years later a small bean-sized tumor appeared just below the popliteal space. A local excision was done, but a recurrence appeared two years later. Five years ago the tumor was again excised. Owing to involvement of peroneal nerve, foot-drop followed this procedure. One year ago, a second recurrence was treated by wide excision. The patient had been moderately dyspneic for the past four months. X-ray films taken April 1, 1936, showed extensive chest metastases.

Pathologic Report.—Synovioma.

Irradiation.—Patient was given 400 r. units to each of four portals in left chest. *Factors:* 198 K.V. 70 cm. Field: 14 × 14 cm.

Course.—Patient died of chest metastases on April 3, 1936.

CASE 15.—F. K., a forty-four-year-old Jewish housewife, was admitted to the Memorial Hospital on Jan. 20, 1936, service of Dr. George Pack. One year before her admission she noticed a painless swelling on the medial aspect of the dorsum of the left foot. There was no history of trauma. Six weeks before admission the tumor was excised, but there was a prompt recurrence which necessitated excision again five weeks later. A pathologic diagnosis of sarcoma was made at another hospital, and the patient was referred to the Memorial Hospital. Examination on entry revealed a painless, infected, fungating tumor on the medial aspect of the left foot, anterior and below the ankle. There was no adenopathy. Films of the chest taken on Jan. 22, 1936, showed no evidence of metastasis.

Pathologic Report.—Synovioma.

Irradiation.—Patient has received 80,000 mg. hr. from Jan. 28, 1936, to Feb. 11, 1936, to one portal (left ankle mesially), using the 4 gram element pack at 10 cm. distance.

Course.—On April 4, 1936, inflammation had subsided and the incision had healed, but regression of the tumor had not been satisfactory.

ETIOLOGY

Of the predisposing factors, age is of negligible significance, as is shown by the fact that the youngest in this group was an infant nine months old, while the oldest patient was sixty-four years of age. Race as a factor may be dismissed as having no further bearing on etiology. The sex incidence is, however, of some interest, in that 4 of the 13 cases reported occurred in women, whereas 9, or more than two-thirds, were in men. Stewart[3] mentions the possibility that inflammatory changes in a chronic synovitis might be held accountable for the neoplastic development in some of these tumors. In only one of our cases was there a preexisting inflammation that might be considered as a possible etiologic factor. One, of course, cannot say what influence trauma may have had toward inducing inflammatory, hyperplastic, or perhaps neoplastic, changes in 6 of our cases.

SYMPTOMS AND PHYSICAL SIGNS

In early cases pain may be the only complaint. This is described as being dull, aching in character, and is particularly aggravated by weight-bearing. One author suggests that this is evidence of invasion

of the periosteum, but it should be borne in mind that the synovial lining of joints is very sensitive, and when these structures are inflamed or compressed, severe pain results.

Joint function is often surprisingly unimpaired and bone is not usually involved, so that radiographic examination may be entirely negative. Wagner,[17] however, has called attention to the fact that if films are made for soft tissue detail, the presence of the tumor may be revealed, and this was demonstrated in one of our cases. Knox states that in some cases joint tuberculosis may be simulated. As a rule, physical signs in early cases are of little aid, and the lesion is discovered at operation, which is usually an exploration, its true nature not being suspected until the pathologist examines the tissue.

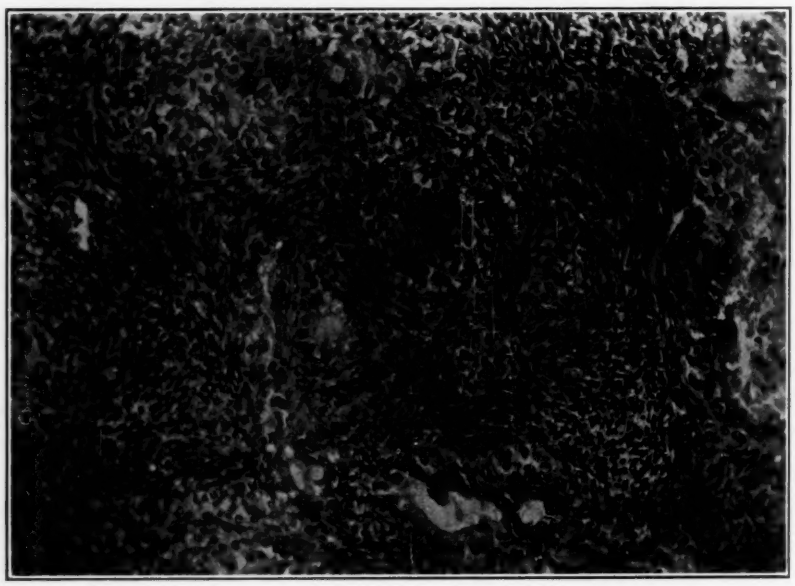

Fig. 1.—Section of synovioma showing typical glandlike structure (×150).

Aspiration biopsy should prove of value in the diagnosis, but so far as we know, it has not been used in any of the cases reported.

DIFFERENTIAL DIAGNOSIS

Diagnosis is often exceedingly difficult. Where no palpable tumor exists, it may be impossible until operation has disclosed the condition. Where a definitely palpable tumor exists, it must be differentiated from other soft part tumors, such as fibrosarcoma, myosarcoma, neurogenic sarcoma, liposarcoma, and xanthosarcoma of tendon sheath origin. The tumor is usually firm, well circumscribed, homogeneous, is not particularly tender, and occurs most frequently near the knee joint. Other joints involved are those of the fingers, ankle, and metatarsus. We have not seen the condition in the hip, elbow, or shoulder

joints and, so far as we know, no case has been reported in the literature. Adenopathy almost never occurs. It should be emphasized that physical signs are of little aid in the diagnosis, which is determined definitely on biopsy.

TREATMENT

The clinical course of synovioma varies with respect to the histologic features and to the type of treatment employed. Some show a microscopic picture that indicates a low grade of malignancy, while others, with much more malignant features, not only tend to recur promptly, but even give rise to pulmonary metastases.

Irradiation.—While irradiation has been employed, it is generally accepted that these tumors are not radiosensitive. In two of Smith's[15] cases the cutaneous and pulmonary metastases were only temporarily improved. One of Wagner's[17] cases was treated by F. C. Wood for a period before consent to amputation was obtained, and during this time the growth slowly extended into the head of the tibia. Knox[8] reports a case having pulmonary metastases treated by irradiation with no improvement. Of the Memorial Hospital cases only one showed regression following irradiation. This was a synovioma of the finger that received intensive treatment. Thus far it would seem that for operable cases, treatment solely by irradiation is scarcely justified.

Surgical Excision.—Owing to the fact that the true nature of the process is so seldom appreciated until after the sections have been examined, the initial operation is often undertaken lightly, and the excision may be inadequate. Moreover, the anatomic location of the tumor may make it difficult to remove as much pathologic tissue as desirable. Once the tumor has recurred, it is not likely to yield to further conservative operation, and resort to a radical procedure, such as amputation, is necessary.

Preoperative irradiation followed by excision is not often attempted, since the diagnosis is generally arrived at only after a local removal, and tissue study has been done. At present, it is our opinion that any operable tumor, which, by its location, suggests the probability or even the possibility of synovioma, should have a wide excision. If histologic study confirms this diagnosis, then postoperative irradiation by fractional dose x-ray may be advisable. If the recurrence should follow, an amputation is then in order, provided the lungs are free from metastases. But if the diagnosis has been established, and the local excision is impractical or impossible, amputation seems justified. Where no operation is feasible, or where it is refused by the patient, x-ray therapy or radium pack treatment is suggested.

Our experience with postoperative injections of Coley's toxins for synovioma is insufficient to permit of an expression of opinion as to

their possible value as a prophylactic against recurrence or metastases. The similarity of the lesion to other endotheliomas would suggest that they be given further trial in conjunction with postoperative irradiation. In this connection it may be noted that one of the five-year survivals developed erysipelas while under treatment.

TABLE I

CASES SURVIVING FIVE YEARS OR MORE—MEMORIAL HOSPITAL SERIES

NAME	METHODS OF TREATMENT	FINAL NOTE
J. C.	Local excision; irradiation; patient developed erysipelas	Six-year survival; no evidence of recurrence
M. D.	Local excision; irradiation	Five-year survival; no evidence of recurrence
J. M.	Local excision; irradiation	Seven-year survival; died of pulmonary metastases

TABLE II

COLLECTED SERIES FROM LITERATURE

NAME	METHODS OF TREATMENT	FINAL NOTE
Marsh	Local excision; amputation	Alive
Faulkner	Local excision; irradiation	Alive
Wagner, L. C.	Local excision; irradiation; Coley's toxins; amputation	Dead (ten-year survival)
Knox, L. C.	Local excision; amputation	Dead (six-year survival)
Coley, W. B.	Local excision (3 attempts)	Dead (seven-year survival)

TABLE III

END-RESULTS OF SYNOVIOMA CASES—MEMORIAL HOSPITAL SERIES

NO.	NAME	AGE	SEX	METHODS OF TREATMENT	PERIOD OF SURVIVAL	DEAD OR ALIVE
1	H. M.	45	M	Local excision; irradiation	18 months	Alive
2	J. C.	9 mo.	M	Local excision and irradiation; patient developed erysipelas	5 years	Alive
3	V. C.	24	M	Local excision and irradiation	2½ years	Dead
4	L. B.	35	M	Amputation	4 years	Alive (dying of pulmonary metastases
5	M. S.	22	F	Local excision and amputation	13 months	Dead
6	M. T.	47	M	Local excision; amputation; irradiation	3 years	Dead
7	F. G.	35	F	Local excision; irradiation	18 months	Alive
8	N. C.	12	F	Local excision; amputation; irradiation	4 years	Alive
9	I. S.	64	M	Local excision; amputation; irradiation	4 years	Alive
10	M. P.	27	M	Local excision; irradiation	1 year	Alive
11	A. H.	16	F	Local excision; irradiation; Coley's toxins	3½ years	Alive
12	M. D.	45	F	Local excision; irradiation	5 years	Alive
13	M. G.	45	M	Local excision	6 months	Alive
14	J. M.	29	F	Local excision; irradiation	7 years	Dead
15	F. K.	44	F	Local excision; irradiation	6 months	Alive

Considering the cases as a whole, we believe that in the past, the early treatment had been too conservative and radical surgery instituted too late in the course of the disease. If treatment were more radical at the outset, the results might be improved.

PROGNOSIS

Of the 20 case reports in our review of the literature, 18 were followed for periods varying from six months to ten years. Of these, 1 survived ten years, finally dying of pulmonary metastases; 4 survived five years, and 3 lived three years. Of the remaining cases, 4 died in less than three years, and the other 6 still survive. Of our patients, only 3 are five-year survivals.

TABLE IV

END-RESULTS OF SYNOVIOMA CASES PREVIOUSLY REPORTED IN LITERATURE

NO.	REPORTED BY	AGE	SEX	METHODS OF TREATMENT	PERIOD OF SURVIVAL	DEAD OR ALIVE
1	Hardie and Salter	25	M	Amputation	1 year	Alive
2	Lejars and R. Duval	22	M	Local excision; amputation	1 year	Dead
3	Marsh	21	M	Local excision; amputation	6 years	Alive
4	Razemon and Bizard	22	M	Local excision (wide)	2 years	Alive
5	Lockwood	24	F	Resection of knee joint	-------	Died (surg. shock)
6	Faccini	—	—	Local excision; amputation	1 year	Alive
7	Wegelin	28	M	Local excision	6 months	Alive
8	Turner	28	M	Local excision	Not followed	
9	Chenot and Tzanck	38	F	Local excision	Not followed	
10	Smith, L. J.	24	M	Local excision; irradiation following recurrence	3 years	Dead
11	Smith, L. J.	35	M	Local excision; irradiation; amputation	2½ years	Dead
12	Wagner, L. C.	35	M	Local excision; irradiations; toxins, amputation	10 years	Dead
13	Wagner, L. C.	15	F	Local excision	3 years	Alive
14	Faulkner	49	F	Local excision; irradiation	6 years	Alive
15	Faulkner	28	F	Local excision	4 months	Alive
16	Knox, L. C.	—	F	Local excision; amputation	6 years	Dead
17	Knox, L. C.	33	M	Local excision; amputation	3 years	Dead
18	Knox, L. C.	24	M	Local excision; amputation	2½ years	Alive
19	Hodgson and Bishop	28	M	Biopsy; irradiation; amputation; Coley's toxins; local excision	7 months	Dead
20	La Ferla and Demelas	17	M	Local excision	3 years	Alive

Combining our results with those in the literature, we have 6, or 20 per cent five-year, and 13, or 40 per cent three-year survivals. We know of none who has survived more than ten years, and therefore can only conclude that with the present mode of treatment, life expectancy is certainly not more than this, while in two-thirds of the patients, it is less than five years.

SUMMARY

A study of reported cases of synovioma and others observed at the Memorial Hospital comprises the 20 followed cases in the literature and 15 in our series. The knee is the most frequent site. No single etiologic factor is apparent. The diagnosis is seldom made until biopsy reveals it. There is a wide variation in the degree of malignancy, rapidity of dissemination, and life expectancy.

Treatment thus far has been very disappointing. These tumors are radioresistant. We do not favor preoperative irradiation. Amputation is recommended unless wide excision is still practicable, and for recurrence, unless a second more radical excision seems feasible. Toxin injections may be tried as a prophylactic measure in addition to surgery and postoperative irradiation. Thus far early treatment has been too conservative, rendering later radical measures ineffectual.

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Editorials

Carcinoma of the Lung

THE introduction and employment of a new technic or of some new method in the treatment of any given disease never fail to create a renewed interest in that syndrome, although for many years its pathologic basis may have been recognized. In this way any new diagnostic or therapeutic measure is, as a rule, responsible for what might be termed "a wave of increase" in our comprehension of many disease syndromes. It is so often true that our knowledge of some well-known clinicopathologic entity remains stationary until some new diagnostic or therapeutic measure is invoked which renders possible the successful treatment of previously unsatisfactory cases. Thus, it may be said that medical history is at the present time repeating itself in regard to the diagnosis and treatment of carcinoma of the lung, and it is of interest to note that in the last three years a renewed enthusiasm in dealing with this condition has been awakened. One need only refer to the earlier textbooks on medicine and, although to a much less extent, on surgery, to realize that formerly the diagnosis of carcinoma of the lung was practically never made until extrapulmonary extension of metastases was clinically recognized and the morbid process was too far advanced to contemplate or justify anything more than simple palliative treatment.

As a matter of fact, most of the symptoms and signs which have been attributed to carcinoma of the lung in reality have been due to carcinoma of the structures involved by regional and remote extensions of the growth from the site of its primary origin. In other words, the clinical syndrome described by earlier writers has consisted of signs and symptoms referable not only to involvement of the lung itself but also to lesions in the surrounding structures and organs. Naturally, then, the correct diagnosis was never or hardly ever made until the disease was obviously incurable by any means or methods known in former times.

In the last few years, however, improvement in our diagnostic methods as well as in our operative technic now renders it possible not only to make an early diagnosis of malignant pulmonary tumors but also to remove a portion or the whole of the lung from a patient in whom such an early diagnosis of malignant tumor has been made, and as a result the clinician can find at the present time more than

mere academic interest in making an early diagnosis of malignant tumors of the lung or other neighboring structures. The increasing number of successful operations performed and reported in the surgical and medical literature for the removal of the lung for carcinoma bears witness to the prompt and enthusiastic response on the part of the clinician to this therapeutic advance. Medicinal and radiation therapy had provided measures of relief, but for many cases these were only temporary and in some of no value at all.

In the past, the occurrence of hemoptysis was considered, in the great majority of cases, to be due to pulmonary tuberculosis until proved to be otherwise, whereas at the present time the presence of blood in the sputums calls for an immediate and careful examination by various modern methods. In other words, at the present time the burden of proof is now on the man who says that this blood spitting is due to tuberculosis and is not a manifestation of growth in the lung. Our clinical pace must be quickened, for until recently the great majority of recognized affections of the respiratory tract have been those in which Time was felt to be the Great Healer, but with the development of methods by which patients cannot only be relieved but cured of malignant neoplasms of the lung it may be said that Time now takes on the rôle of executioner. Successful surgical treatment of carcinoma of the lung depends on an early diagnosis, for malignant tumors in this region masquerade very often as inflammatory affections, specific or nonspecific, and are often hidden under the guise of less serious conditions.

It should also be noted that due to the movement of the entire organ throughout the respiratory cycle, neoplasms arising in the smaller bronchioles or the parenchyma of the lung itself are likely to be disseminated throughout the body at a rather early stage because of the constant motion or milking action or respiratory massage of the growth. While it is true that growths of the primary bronchi in which there is little if any motion are rather slow growing and perhaps late in metastasizing, quite the opposite condition prevails in the tumors arising in the periphery of the lung.

The successful treatment of carcinoma of the lung does not differ in any way from the successful treatment of carcinoma elsewhere in the body. The sine qua non of the proper treatment of malignancy consists in total removal of the organ involved with its attendant lymphatic glands. The lung, like the breast, is an organ which can be removed in its entirety without incapacitating the individual upon whom the operation has been performed. The absence of one lung is not incompatible with a vigorous and active life, for there occurs a compensatory dilatation of the remaining lung which restores the pa-

tient's cardiorespiratory balance almost to its preoperative state. Partial pneumonectomy or lobectomy for carcinoma of the lung has been advocated by some, and unquestionably lobectomy must be taken into consideration when the condition or age of the patient may discourage the idea of a total pneumonectomy, or in case it is thought advisable to perform the total pneumonectomy in two stages. In this manner it may be possible and advisable to remove the affected lobe in the first stage through one incision or approach, and later through an entirely different incision remove the remaining lobe or lobes and the mediastinal lymphatic glands, the condition of the patient being "built up," as it were, between stages.

The removal of one lobe at a time presupposes, of course, that the location of the new growth is in a position far enough removed from the hilus of the lung to permit such an operative procedure. If, on the contrary, the tumor is situated well up in the primary bronchus toward the bifurcation of the trachea this type of a two-stage operation cannot be performed. At the present time in practically all patients over forty-five years of age, a more ideal type of multiple stage total pneumonectomy is employed. This procedure consists, in the first stage, of the ligation of the main branch of the pulmonary artery, either the right or the left, depending on which lung is to be operated upon, before it enters the hilus. Following this any adhesions present are divided as well as the pulmonary ligament up to the level of the inferior pulmonary vein. The chest is then closed with the entrapped air. After one to three weeks, or as soon as the patient's pulse, respirations and temperature have returned to normal, the thorax is reopened through the same incision and the lung is removed. In this manner time is provided for the patient to become adjusted to postoperative changes in the circulatory as well as the respiratory mechanisms. The circulation through the bronchial artery and pulmonary veins prevents the occurrence of gangrene of the lung. There is thus brought about a marked shrinkage in volume of the lung which becomes nonair-containing and relatively avascular. The secondary amputation of the entire organ is thus facilitated for the operator and is much less of a shock for the patient. This method of a multiple stage total pneumonectomy permits the gradual readjustment of the patient as a whole to the changed intrathoracic conditions brought about by throwing one entire lung out of function. This adjustment of the patient as a whole includes many imponderables involving the cardiorespiratory mechanism which are unknown at the present time, but also includes some obvious mechanical alterations which can be observed; i.e., the elevation of the diaphragm on the operated side; the gradual and slight shifting of the mediastinum toward the operated side; the approximation of the ribs with the re-

sultant diminution of the thoracic cage; and finally the decrease in the diameter of the primary bronchus to the operated side as a result of disuse atrophy. All of these factors tend to minimize the danger of the final amputation of the lung and at the same time expedite the obliteration of the remaining thoracic dead space and the healing of the primary bronchus. On account of the greater embarrassment resulting from sudden rotation and displacement of the heart to the right than to the left side of the chest, this type of multiple staged procedure is particularly well adapted to total right pneumonectomy. The method is a safe procedure for older individuals and may in the end prove so for all ages. The first-stage ligation, and pneumolysis if necessary, does not in any way, as in so many instances in surgical two-stage operations, complicate the second stage. On the contrary the latter is made far more simple.

The many ways by which a malignant tumor of the lung may extend is well known. The incompleteness of the fissures between the lobes of the lung renders it highly improbable that a malignant tumor large enough to be detected by an x-ray shadow out in the periphery of one lobe of the lung would be confined solely to that lobe. Therefore lobectomy in such a case would be harmful rather than beneficial to the patient, whereas in this type a total pneumonectomy might readily afford a complete cure. If, on the other hand, the tumor is located in the primary bronchus or close to this region, it will more than likely be anatomically impossible to remove it unless a total pneumonectomy is performed. The lymphatic glands cannot be properly dissected out from the primary bronchi or mediastinum unless a total pneumonectomy is done. The lobes of the human lung are not completely separated and therefore when it be said that a so-called "lobectomy" has been performed, what is meant is that a partial lobectomy or, better still, a partial pneumonectomy was done. This, of course, is not by any means the ideal type of operation for the cure of a malignant tumor of the lung, because the part of the affected lobe left behind is that portion toward which the lymphatic vessels drain. The parenchyma of the affected lobe remaining may also be invaded, although this cannot be determined in the gross by palpation. The same may also be applied to total pneumonectomy. Total removal of the lung means that the entire organ has been removed; i.e., that the primary bronchus has been divided before entering the hilus of the lung, and that the pulmonary artery and veins are likewise ligated individually before entering and after departing from the pulmonary parenchyma. When a tourniquet or temporary ligature has been applied grossly to the entire pedicle and the lung allowed to slough off, or when the operator has cut through lung tissue distal to the tourni-

quet thus leaving behind a stump of lung, the extent of which varies or is unknown, such cases should not and will not be classified in the final adjudication as instances of total pneumonectomy. Such a procedure is not only unsurgical from a technical standpoint, but is almost certain to be attended by a prompt recurrence of the disease process. The patient is thus not only subjected to an unnecessary operation without hope of cure but also loses the one chance for relief which a careful dissection of the mediastinal glands together with the removal of the entire diseased organ may afford. It may therefore be stated with confidence (a) that total pneumonectomy is certainly the operation of choice for the cure of the patient with primary carcinoma of the lung; (b) that if a multiple-staged operation seems advisable the more desirable procedure would apparently consist as a first stage; the preliminary ligation of the pulmonary artery to the affected side, together with the freeing of the lung from any existing adhesions, as well as division of the pulmonary ligament; reserving amputation of the primary bronchus and division of the pulmonary veins for the second stage.

—*William F. Rienhoff, Jr.*
Johns Hopkins University, Baltimore, Md.

The Improper Use of the Word "Drain"

THE word "drain" has been variously defined as "a tube used to promote the escape of fluids from an abscess or wound," to that of "a tube providing a channel for the escape of fluid from a viscus such as the urinary and gallbladder or from the thoracic cavity." A tube inserted into the stomach or jejunum for feeding purposes might also be included as well as an enterostomy or colostomy tube for the removal of fecal material proximal to an obstruction of the bowel. The term "drain" becomes even more confusing when applied to the various tissues and combinations of gauze with rubber or gutta-percha containers that are used in the abdominal cavity to localize or cause to be isolated a certain area of infection, inflammation, or postoperative region that it is felt desirable to have "walled off" from the remainder of the abdominal cavity. From the construction of these various setons or wicks alone, the inappropriateness of the term "drain" is obvious. The only fluid that can escape through them will be a small amount by capillary attraction, "blotted up," so to speak, by the gauze for the first few minutes or hours following their employment. After this short period they become perfectly inert foreign bodies which, by their shape and size, result in the formation of a sinus tract by preventing tissue from interceding between the area to be isolated

and the exterior of the abdominal cavity. These structures do not permit fluid to escape through them as a true drain should. It is felt, therefore, that these wicks should be referred to as *"isolaters"* or *"localizers"* to be distinguished from a true drain. This point is made not only for the sake of academic or scientific accuracy but also because it implies at once the fundamental reasons behind the different uses of the isolater and the drain which not only may aid in the more proper teaching of future surgeons but also may improve the selection of various materials at present used for the accomplishment of isolation in the abdomen.

—*William F. Rienhoff, Jr.*

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

RECENT ADVANCES IN NEUROSURGERY

COBB PILCHER, M.D., NASHVILLE, TENN.
(From the Department of Surgery, Vanderbilt University School of Medicine)

Part I

INTRODUCTION

> Die Hirnchirurgie hat der gemeinsamen Arbeit von Anatomen, Physiologen und Neurologen einen ungeahnten Aufschwung zu verdanken. . . .
>
> —*Fedor Krause*, 1908.[1]

> By slow processes we have come to broaden our horizon, but we do not for a moment forget that we are merely standing on the clustered shoulders of those here unnumbered and unnamed persons who laboriously worked out for the benefit of our generation the development and finer anatomy of the brain, who discovered the localization of its functions, untangled the pathways of its impulses, determined the clinical expression of its lesions, bequeathed to us the instruments we depend upon, laid the foundation stones of modern craniocerebral surgery and more besides.
>
> —*Harvey Cushing*, 1926.[2]

NEUROSURGERY is still a youth among the medical and surgical specialties, and, as such, its development continues to be rapid, its complexion to change almost from day to day. Brilliant investigation, bringing newer knowledge; improved diagnostic adjuncts; valuable technical methods; careful studies of large series of cases—these things and others steadily broaden the scope and improve the accomplishments of neurosurgery. While this paper deals primarily with some of the more recent of these developments, it is fitting that brief tribute be paid to those stalwart forbears without whose abilities and efforts neurosurgery could not have attained its present stature.

Its ancestry extends into antiquity, but neurosurgery is essentially a child of the twentieth century. It inherited from Magendie and Pacchioni, from the Munros and Astley Cooper, from Virchow and Oppenheim and Charcot and a host of others. The first fetal heartbeats became perceptible with McEwen's attack on brain abscesses in the

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1880's, and labor definitely set in with the early operations of Godlee and Horsley and Keen (while anxious accoucheurs like Bennett and Gowers directed the labor!), but with the later days of Victor Horsley in England and the early days of Harvey Cushing in America, neurosurgery may truly be said to have been born.* A few others soon joined in contributing to its development, and gradually its growth became more rapid, its field of interest wider, its adherents more numerous. Most of these early neurosurgeons have continued to make valuable contributions to the subject, and many of these will presently be mentioned.

To include in this brief article all of the valuable and important papers even of the last few years is manifestly impossible. The material included has been selected with the purpose of giving the non-neurosurgical reader a broad view of modern clinical neurosurgery by pointing out the established improvements it has made in recent years. It is obviously true that many interesting cases have been reported, much valuable experimental work done, and numerous operative procedures, whose worth will be proved in the future, have been proposed. Many such important papers have of necessity been omitted.

I. NEUROPHYSIOLOGY AND NEUROLOGIC DIAGNOSIS

In the vast literature on recent neurophysiologic research, investigations in several laboratories and clinics on two subjects bear particularly great clinical diagnostic importance. One group of studies is concerned with the broad significance of, and the localization of function in, the autonomic nervous system, the other with the functions of the cerebral cortex, and particularly of the frontal lobes.

As the culmination of a brilliant series of investigations, Cannon[6, 7] revived Claude Bernard's[8] long-overlooked concept of the milieu intérieur, the "internal environment" of the body. Cannon showed that this complex internal mechanism is primarily under the direction of the autonomic nervous system† and, secondarily, of the endocrine glands. He proved that the automatic protective phenomena associated with emotional disturbances (such as the pilomotor stimulation of rage or fear) are directly dependent on the autonomic system, and he called the harmony autonomically maintained in this automatic internal mechanism, "homeostasis."

Meantime, Cushing, long interested in the hypophysis, began to assemble evidence, clinical and experimental, pointing to the existence of a suprahypophyseal (hypothalamic) parasympathetic center, or centers, apparently directly under the influence of posterior hypophyseal secretion. Conversely, this hypothalamic area appeared to

*Adson[3] calls McEwen the "father" of neurosurgery, and Cushing[4] states that Horsley's famous operation for cord tumor[5] marks its birth.

†An interesting account of the early history of knowledge of the autonomic nervous system has recently been published by Sheehan[9].

exert direct neural influence upon the hypophysis. In support of this concept were the previous observations suggesting a "portal" circulation from pituitary to hypothalamus of Popa and Fielding,[10, 11] and the experiments of Beatty[12, 13] and his coworkers on the visceral effects of stimulation, or destruction of the pretuberal hypothalamic area, or of decerebration at levels eliminating various hypothalamic nuclei. Cushing's papers on this subject[14-16] were finally published together in a volume entitled "Pituitary Body, Hypothalamus, and Parasympathetic Nervous System."[17] The subsequent observations of Watts and Fulton,[18] and Hoff and Sheehan[19] upon the visceral effects of anterior hypothalamic lesions were in accord with the hypothesis just described.

Similarly, the observations of Bard,[20] and Beatty,[12, 13] a more recent careful series of studies from Ranson's[21-27] laboratory, and important investigations by Keller,[28, 29] Fulton and Ingraham,[30] and many others (see Fulton,[31] Bard,[32] and the papers cited above) have even more definitely proved the existence of centers for sympathetic control in the hypothalamus (probably in its posterior nuclei).

Thus, it has been experimentally established that in the hypothalamus lie subcortical autonomic "centers" which influence or control cardiac and vasomotor function, gastrointestinal and other abdominal visceral function, endocrine function, temperature regulation, sleep, and similar phenomena of the "internal environment." Cushing's revival of the concept of a possible neurogenic basis of peptic ulcers[16] introduces only one of the widespread and fascinating problems upon which new light has been thrown.

Clinically, this localization of autonomic function has been supported by the cases reported by Cushing,[17] Penfield,[33] McLean,[34] Masten and Bunts,[35] and Davison and Selby.[36]

The second great series of physiologic studies, that dealing with the functions of the frontal lobes, has emanated largely from Fulton's Laboratory of Physiology at Yale. Conducted almost exclusively on primates, these experiments are remarkable for their carefully planned completeness, as well as for their important physiologic discoveries.

The results of this work were summarized in a symposium[37-41] at the Cleveland Meeting of the American Medical Association in 1934 and in Fulton's Beaumont and Ludwig Hektoen Lectures.[42, 43] On functional and structural grounds,[37, 44, 45] the frontal lobes are divided into the "motor area" (motor cortex, area of Betz cells, area 4 of Brodmann), the "premotor area" (area 6 of Brodmann), and the "frontal association area" (prefrontal area), and the functions of each have been carefully studied. In brief summary, the motor area is the cortical center for direct voluntary control of simple movements, and its destruction results in flaccid paralysis and the signs of Babinski and Chaddock.[46] The premotor area controls complex integrative muscular movements[47] and is the cortical center for many autonomic func-

tions (such as vasomotor control[40] and intestinal movements[41, 48]). Its destruction produces spasticity, loss of complex movements, temporary "forced grasping,"[49] and vasomotor disturbances.[38] The frontal association area is concerned with intellectual function. It is of great interest that the impairment of this function (especially loss of recent memory and inability to learn) is dependent upon destruction of the prefrontal area on both sides.[39]

This localization of function has been opposed by Walshe,[50, 51] but has gained clinical support from Spurling,[52] Penfield and Evans,[53] Kennard, Viets, and Fulton,[54] German and Fox,[55] Brickner,[56] and Bucy.[57]

Space permits only brief mention of the valuable studies on the visual mechanism by Poljak,[58-60] Spence and Fulton,[61] Penfield, Evans and McMillan,[62] Ranson, Magoun and their coworkers,[63-67] and Merritt and Moore.[68] The interesting observations on the electric potential discharge from the cerebral cortex by Berger,[69] Adrian and Matthews,[70-72] Cazzamalli,[73] Gibbs, Davis and Lennox,[74] Foerster and Altenburger[75] and the studies of Elsberg and his associates[76, 77] on the sense of smell give promise of valuable clinical usage.

The description of the syndrome of pituitary basophilism by Cushing[17, 78] has opened a new and still controversial problem in the field of endocrinology.

Other diagnostic studies will be discussed in the following sections.

II. ROENTGENOGRAPHY

Roentgenography has long been an essential adjunct to neurosurgical diagnosis. Plain stereoscopic views of skull and spine show evidences of increased intracranial pressure, of local changes in the skull and spine, and of intracranial calcification (cf. Davis[79] and Sosman[80]). The "pineal shift" (Naffziger[81]) serves to lateralize many expanding lesions, and Camp, Adson and Shugrue[82] have demonstrated important roentgenographic changes in the spine which are associated with spinal tumors.

The introduction of ventriculography and encephalography by Dandy[83-86] in 1918 further enhanced the value of roentgenography to the neurosurgeon. Ventriculography was almost universally adopted at once, and many papers concerning it have been published (e.g., Grant,[87] Pilcher and Wilson,[88] Davis,[79] Adson,[89] Fincher,[90] Elsberg and Silbert.[91, 92] In 1933, Jessen,[93] and Schoenfeld and Freeman[94] independently reported the use of an opaque medium (thorium dioxide) for ventriculography, and the latter authors subsequently supplemented their first paper by reporting the use of the method in "about twenty cases."[95] Meanwhile, Twining and Rowbotham[96] (1935) reported the same procedure in two cases, without apparently being aware of its previous use. That the method is not without

danger, however, is shown by the reports of Shih and Jung,[97] who experimentally produced thrombocytopenic purpura by the intravenous injection of thorium dioxide in rabbits, and Alexander, Jung and Lyman,[98] who found ependymal inflammation after its introduction into the ventricles.

Encephalography following spinal air injection had been relatively little used (especially in this country) until interest in it was renewed by Pancoast and Fay[99, 100] in 1929. Its value has been greatly increased and its use popularized by a recent series of studies by Dyke and Davidoff,[101-110] who have delineated normal structures and pointed out important diagnostic encephalographic findings.

A recent innovation is cerebral arteriography, introduced by Egas Moniz,[111, 112] of Lisbon, in 1927. In this procedure, an opaque substance (Moniz first used strontium bromide or sodium iodide, but has recently advocated colloidal thorium dioxide[113]) is injected into the internal carotid artery, followed at once by the rapid exposure of a series of skull films. Moniz and his associates have published numerous papers on the subject in several languages.[114-119] They have recently reported the injection of thorotrast into both carotid arteries at the same time.[120] Dott,[121] and Worms and Bretton[122] have used the method, and Lohr and Jacobi[123, 124] have advocated combining arteriography with pneumoencephalography.

The present field of usefulness of cerebral arteriography must be considered limited by its potential danger, its difficulty of interpretation, and its restricted visualization of intracranial structures.

III. OPERATIVE NEUROSURGERY

The highly specialized technic of craniocerebral operations, still adhering to the early principles of Cushing, Krause, Frazier, and their contemporaries, has, nevertheless, developed remarkably during recent years. Outstanding among the many contributions has been the introduction by Cushing[125, 126] of the high frequency, damped-wave electrosurgical unit devised by Bovie.[127] By facilitating hemostasis and making possible bloodless incision of cerebral tissue, this device has greatly added to operative ease, speed and safety. Other improvements in general operative technic have been the "myoplastic" operation of Penfield and Cone,[128] the scalp clips of Adson and Fincher,[129] the incisions for unilateral and bilateral transfrontal exploration of Sachs,[130, 131] the exposure of the facial canal of Tremble and Penfield,[132] Naffziger's orbital decompression for exophthalmos,[133] and combined occipitocerebellar exposure,[134] and the delayed nerve-graft method of treating facial palsy of Duel.[135] Excellent descriptions of general operative technic have been written by Adson,[3] Sachs,[130] Dandy,[136] and others.

New operations have been devised for the treatment of many special conditions and these will be discussed in succeeding sections.

IV. NEUROPATHOLOGY

During the past ten years, enormous strides have been made in the field of neuropathology, based largely upon the brilliant development of metallic staining methods by Ramón y Cajal and his pupils.[137] In 1926, appeared the now classical monograph by Bailey and Cushing,[138*] in which the gliomas were classified on a histogenetic basis. It was shown that the different types of glioma varied greatly in their most frequent sites of origin, their rapidity of growth, their amenability to surgical removal and in the survival periods of their victims. Thus, it became possible in many cases to make presumptive preoperative and accurate operative histologic diagnoses, to vary the operative procedure with the type of lesion encountered, saving many patients from useless, mutilating operations, and to predict the likelihood and probable time of postoperative recurrence and the susceptibility of the tumor to roentgen therapy (cf. Section VII).

Numerous studies of the various glioma types have further simplified and clarified the classification. Among these may be mentioned the papers of Globus and Strauss[141] on spongioblastoma multiforme (now called glioblastoma),† of Bailey and Cushing[142, 143] on the medulloblastomas, of Cushing[144] on the cerebellar astrocytomas, of Bailey and Eisenhardt,[145] and of Pilcher[146] on the spongioblastomas, of Bailey and Bucy[147] on the oligodendrogliomas, of Bailey,[148, 149] and Fincher and Coon[150] on the ependymomas, and of Horrax and Bailey[151, 152] on the pinealomas. Beautiful illustrations of the gliomas have been published by Bailey,[153, 154] and Roussy and Oberling.[155] Kernohan[156, 157] has made important contributions to our knowledge of spinal cord gliomas.

In a similar manner, the pathologic nature of the fibroblastic tumors arising from the leptomeninx and the cranial nerve sheaths has been carefully studied by Penfield,[158, 159] Cushing,[160] Phemister,[161] Roussy and Cornil,[162] Rhoads and van Wagenen,[163] Craig,[164] Kolodny,[165] and Bailey and his associates.[166-169] The pathology of the tumors of the blood vessels of the brain has been fully discussed by Cushing and Bailey,[170] and by Dandy.[171, 172] Space does not permit mention of the many papers dealing with less common tumors. They are discussed in detail in Penfield's monumental "Cytology and Cellular Pathology of the Central Nervous System,"[173] which was published in 1932 and contains contributions by internationally recognized authorities on the various subjects. An excellent monograph on neuropathology has also been published by Freeman.[174]

In addition to the rapidly advancing knowledge of the pathology of tumors, equally important contributions have been made regarding

*It must not be forgotten that previous tentative classifications had been proposed in England by Greenfield[139] and in France by Roussy, Lhermitte, and Cornil.[140]

†This paper preceded the publication of the monograph of Bailey and Cushing.

the reaction of the brain to inflammation and injury by Penfield and his associates.[159, 175-178] The peculiar pathology of subdural hematoma has been greatly clarified by the studies of Putnam,[179] and Munro and Merritt.[180] (Also cf. Sections VI, VII and IX.)

Two new methods of pathologic examination have been introduced into the study of intracranial tumors; namely, tissue culture by Kredel,[181, 182] Buckley,[183] and Russell and Bland,[184] and the supravital preparation by Eisenhardt and Cushing.[185, 186] The latter is a valuable supplement to the previously employed frozen section method of immediate histologic diagnosis at operation.

(Part II will appear in the next issue of SURGERY.)

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Review of Recent Meetings

REVIEW OF THE SIXTH CONGRESS OF THE INTERNATIONAL SOCIETY OF UROLOGISTS

FRANK HINMAN, M.D., SAN FRANCISCO, CALIF.
(From the Division of Urology, University of California Medical School)

THE Sixth Congress of the International Society of Urologists was held in Vienna on September 8 to 12, 1936, with a fair representation of members from 33 different nations, despite the unsettled condition of the world. There were present no Spaniards or Russians, and only 14 of the total American membership of 50. However, the international committee has increased the number of representatives for the United States to 75 (probably because of the prompt payment of dues in the past, the surety of which, together with that of Great Britain's members, has been accredited with keeping the international society alive). Membership in the American Association of Genito-Urinary Surgeons has been held by the national committee as a requisite to admission to the international society and with the extension of this privilege to the association's entire membership, a larger representation at the international meetings will undoubtedly result. Few Americans and Britishers, however, are linguists, while other nationalists, as a rule, know one language or more besides their own. The official languages are English, French, German, Italian, and Spanish. The English-speaking factions, thus handicapped, have been unable to exert the influence in the management of the international society to which they are entitled by reason of the proportion of members who attend, pay dues, and have scientific attainments. The disaffection occasioned by this state of affairs has even led to the agitation for the formation of an international society of English-speaking urologists. This somewhat ridiculous outcome was forestalled by the advent in London of the Clinical Society of Urologists, organized similarly to the American society of that name, the two proposing to hold a joint session just before or after the international meeting. (The first joint session was held in London on September 3 and 4, 1936.) Furthermore, the English language has not fared too badly lately since London had the Congress in 1933 and New York will have it in 1939.

On the last day of the Congress, members select, by majority vote, the three main subjects for discussion at the next Congress and the nation in which the Congress is to be held. Each subject is presented by three essayists so that each Congress has nine chief essayists. The country holding the Congress is permitted one essayist for each subject and the remaining six are selected by nation, the membership of which then chooses its representative; no nation, with the exception of the one acting as host, is permitted more than one essayist. Every member of the society, however, may discuss one, two, or all three subjects after their presentation by the three essayists. Since meetings are held every third year, this arrangement gives ample time for preparation (the rule of 3: 3 subjects, 3 essayists, 3 years) and before the meeting the nine chief papers are printed, in the language of delivery, with summaries translated into the four alien tongues and reach the hands of members as a bound volume. This should permit the discussions to be live and pertinent. Unfortunately, often they are neither. To the average member who understands well only his own spoken language, discussions other than those in that language are useless

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since these discussions do not appear in the published transactions. The free use of lantern slides would help, as many who miss the spoken word could understand the written captions. Such a plan is feasible because these discussions usually are prepared in advance of the meeting and are rarely extemporaneous. As matters stand now, it would seem that the member who reads the transactions at home gets as much scientifically as the one who travels long distances to attend. This is true, except for the value of meeting contemporaries whose scientific publications have been read and whose views and conclusions therein presented have been pondered. First-hand acquaintanceship gives the stamp of authority to an impression gained by reading, and the honesty and sincerity—or the superficiality—of the author is established. For his own education, every member should attend at least one meeting, and subsequent attendance may be guided by social rather than scientific benefits, unless he is urged on by actual participation in the program. That it works this way is proved by the fact that four members from the United States who journeyed to London expressly for the clinical meetings there preferred returning home or sight-seeing to going to Vienna. Nevertheless, the scientific value of the International Congress is very great and all meetings since 1919 have been well attended and successful.

The three subjects presented at Vienna were: **I, Die Behandlung des Prostatacarcinoms (The Management of Carcinoma of the Prostate); II, Eiterungen des Nierenparenchyms (Suppuration of the Renal Parenchyma); and III, Physiologie und Pathologie der Nierenexkretion (Physiology and Pathology of Renal Secretion).**

I. Carcinoma of the prostate occurs much more frequently than shown by earlier statistics. The incidence has long been placed as 20 per cent of all cases of prostatism. It is probably more than 30 per cent. This apparent rise is caused not by a true increase, but by the more frequent recognition of cancer. This is particularly true of lesions unsuspected on rectal palpation, the tissues of which show cancer on examination after transurethral resection for supposedly benign median bars and hyperplasias or after surgical enucleation (perineally or suprapubically). Cancer has long been known to occur in two forms: either as a primary condition of the true glands of the prostate, or as a malignant degeneration of the periurethral glands after they have undergone hyperplastic changes. The first form has long been thought to arise mostly in the posterior lobe and gives the sensation of stony hardness on rectal palpation. The second form usually gives no clinical evidence of its presence, the obstructive symptoms being referred, rightly as a rule, to mixed and nonmalignant fibromyoglandular changes. The incidence of the two forms and their pathogenesis have not been well understood.

Hryntschak (Vienna, Reporter for Austria), in collaboration with Bauer, made a careful histologic study of the material removed at 310 prostatectomies for hyperplasia. In 108 of these specimens the tissues were found to be normal but there were areas of regeneration and inflammation in 13, areas of regeneration alone in 34, and areas of atypical regeneration in 67 which took on the appearance of precancerous changes in 20 and true cancer in 24. In the 100 of these 310 specimens which were accompanied with complete clinical notes (personal cases), cancer was found histologically in 12, though it had been suspected clinically in only 4. In 7 others, of the 100 specimens (personal), definite precancerous changes were present. Of the 210 specimens of hyperplasia from outside sources, 12 showed cancer and 13 precancerous lesions. Foci of tubular regeneration, which presumably follow an injury either traumatic or inflammatory, were frequently seen in hyperplasia. When tubules had evidently undergone several regenerative changes, by reason of repeated or continual irritation, these changes had become irregular and atypical so that the authors believe that they saw (demonstrated by photomicrographs) the pathogenesis of cancer

in prostatic hyperplasia. This is identical, they believe, with that of cancer in the true glands of the prostate (such as the nonhyperplastic posterior lobe) and in no case was it an extension of this latter into the hyperplasia. The progressive changes are: inflammation—regeneration (which becomes irregular and atypical on too frequent repetition and then potentially malignant)—precancer—cancer. This theory, they believe, explains the peculiar varieties of prostatic cancer (adenomatous, medullary, scirrhous, and squamous cell), the development of cancer many years after prostatectomy and the occurrence of cancer more than twice as frequently in the true prostatic glands as in the hyperplastic portions of the periurethral glands. It establishes the idea, however, that cancer can occur in any portion.

Nitch (London, Reporter for England) discussed "the conservative treatment of carcinoma of the prostate" under three headings: **Irradiation Therapy, Surgery, and Surgery Combined With Irradiation Therapy.** He regards radium implantation as superior to x-ray therapy, the late results of which are disappointing and which may even cause rapid dissemination of the growth. He applied radium in large doses, 14 mg. to the rectal surfaces, 50 mg. to the vesical surfaces, and 5 mg. to the urethral surfaces and in the few patients thus treated obtained a cure in 28 per cent. Suprapubic drainage, transplantation of the ureters and transurethral resection, he listed as conservative methods of surgical treatment. Curative surgery by radical prostatectomy was admitted to be the ideal but is rarely applicable. He transplanted ureters into the rectum for palliation in two patients and prefers this method to drainage by cystotomy. He concluded that "in the future electroresection followed by some form of radiotherapy will be the method of choice."

Oreja's (San Sebastian, Reporter for Spain, paper read by title) printed discussion is mostly statistical, from the literature, reiterating the well-known fact that cure depends on early recognition and radical removal, and the perineal route is the method preferred by the majority.* Cancer of the prostate is so insidious and slow-growing that statistics from different sources on the relative merits of methods of treatment are not really comparable. Patients have been known to live for twelve or more years after a definite diagnosis of cancer, with no treatment whatsoever. Reports of three-, four-, and five-year cures by radium, x-ray therapy and surgery consequently are compared with difficulty.

II. **Illyés** (Budapest, Reporter for Hungary) analyzed and discussed 1,262 cases of suppurations of the kidney, 1,079 of which came to operation. He classified his patients into three groups:

I. Those with suppurative nephritis (46 cases were discussed).
II. Those with suppurative pyelonephritis (455 cases were discussed).
III. Those with pyonephrosis and renal atrophy (713 cases were discussed).

Two hundred and seven cases (16 operated on) of pyelitis of pregnancy were listed and discussed separately.

In the 41 patients who had unilateral miliary abscesses of the kidney, infection of the blood stream arose in the tonsils in 13, from pelvic infections following abortion in 8, from furuncles in 8, from an abscess following a gunshot wound in one, following pneumonia in one, from appendicitis in 6, and following an abscess of the prostate in one. Three cases were regarded as being lymphogenous in origin (diarrhea prominent before the onset). In 32 of the patients, the kidney was decapsulated and in 6, removed (type of treatment in 3, unstated). Of the 41, all recovered except 2, of whom one died of sepsis and one of myocardial disease.

Five cases of carbuncle of the kidney were discussed, all caused by staphylococcus infection. The reporter emphasized the danger of retrograde pyelography for diag-

*No mention is made of radical prostatoseminal vesiculocystectomy after ureterointestinal implantation.

nosis in these cases because of the greater ease of pyelovenous and pyelo-interstitial backflow, producing septicemia. One of these patients died on the eighth day. In one case the carbuncle was opened and drained. There was a long convalescence with final healing. Nephrectomy was performed for the other three patients and all recovered.

In the group of patients with suppurative pyelonephritis (494), the infection was ascending in nature following urinary obstruction, of which hypertrophy of the prostate, tumors of the bladder, severe chronic forms of cystitis, and strictures of the urethra were the commonest causes. Suppurative pyelonephritis, however, occasionally followed simple catheterization of the ureter or pyelography. In the great majority of instances the organism was the colon bacillus. In a number of cases, unilateral suppurative pyelonephritis followed an obstructing stone in the ureter and in many cases followed renal stone, calculous pyelonephritis being included. Four hundred thirty-four of these patients were operated on. Sixty had bilateral involvement and were not operated upon. In 317 of those on whom surgery was performed, the suppuration was secondary to lithiasis either of the kidney or ureter, an incidence of 17 per cent in the personal cases (total 1,478 renal and ureteral stones). There were 175 nephrectomies for renal calculus and 28 cases of decapsulation after removal of the stone in the ureter. In the remaining 114 cases following obstructions in the lower tract, decapsulation was performed 46 times. In 117 patients, the cause of the pyelonephritis was unknown and in this group nephrectomy was performed in 92 and decapsulation in 25. Of the total patients with suppurative pyelonephritis, 10 died, giving a mortality of 4.3 per cent.

The third group comprised 713 cases of pyonephrosis, 590 of which came to operation; 181 patients were operated upon for primary pyonephrosis; for 174 of these, one-stage nephrectomy was done and, for 7, two-stage nephrectomy—that is, nephrotomy followed by nephrectomy. Ten per cent of the patients operated upon died. Among the 391 patients with secondary pyonephrosis (in 258 instances, secondary to calculus) there was an operative mortality of 8 per cent.

Four cases of atrophic pyelonephritis (pyelonephritischen Schrumpfniere) were mentioned, but the reviewer did not distinguish between atrophic pyelonephritis and fatty degeneration. One patient had renal atrophy with stone, another atrophy of an infected hydronephrosis, in another the condition followed infarction, and the fourth, a man sixty-three years old who had had his prostate removed six months previously, had a true atrophic pyelonephritis secondary to ascending infection.

Cabot (Rochester, Minnesota, Reporter for the United States) discussed in detail the first group cited in Illyés' classification, a group characterized by the infecting organism's being carried to the kidney in the blood stream from peripheral infections, particularly boils, carbuncles and septic wounds of the skin and acute infections of the upper respiratory tract. In a careful study of 46 patients with acute inflammatory processes about the mouth, throat, and ear, 32 showed organisms in the urinary smear, and 18 in culture, whereas, in a group of 10 apparently normal persons used as controls, the studies were negative throughout. The organism was a staphylococcus in most cases; as a rule, this can be recovered in the urine during the acute stage but may be absent later. The diagnostic importance of the limitation of movement of the diaphragm on the affected side and of the normal movements of the kidney, as demonstrated by fluoroscope or pyelography, was emphasized. Diminished visualization of the infected kidney in the excretory urogram has been noted. Four grades of this particular type of infection of the kidney by way of the blood stream may be distinguished clinically: (1) the fulminating group, relatively uncommon, which presents chiefly the complete overwhelming of the patient with a lesion apparently abdominal: pain, fever, rapid pulse, nausea, and abdominal distention are present. (2) The group of acute cases in which there are high fever, marked leucocytosis, and pain referred definitely to the region of the kidney with

local tenderness in the region of the kidney. The third, or subacute group, differs from the second only in the degree of the severity of symptoms and signs. In both of these groups a search of the urine for cocci in the early stages is usually successful. A fourth clinical group is composed of borderline cases in which the clinical picture is ill defined. Pathologically these clinical groups include the diffuse suppurative nephritides, the kidney with multiple cortical abscesses, the renal carbuncles, and perirenal abscesses. As indications for operation are given:

1. The fulminating type of infection.
2. The widespread infection of the kidney in which the patient seems unable to control the disease, as shown by the development of anemia and failing general condition.
3. Massive abscess of the kidney as shown by the pyelogram.
4. Perinephritic abscess.

Necker (Vienna, Reporter for Austria) recognized primary and secondary suppurations of the renal parenchyma without reference to the probable route of invasion. The primary suppurations are rarely diffuse but more often sharply circumscribed lesions of the cortex usually caused by staphylococci and only rarely by streptococci. Necker questioned the occurrence of primary suppurations in the cortex caused by *Bacillus coli*. Coccal lesions starting in the peripheral zones extend to form the clinical groups recognized as the rare diffuse cortical suppurations, the circumscribed miliary abscesses, the boillike carbuncles, the large intrarenal abscesses and the so-called xantholipomatous staphylomycoses. Secondary renal suppuration of the parenchyma usually arises from an infection with *Bacillus coli*. The progressive changes are often influenced in this group by dynamic factors of which pyelorenal backflow is one of the most important. The reviewer believes it is not possible at present to give a true clinical classification of the various types of cortical suppuration except possibly of the carbuncle.

III. Two of the reporters on the main subject, the physiology and pathology of renal excretion, confined their discussion mainly to hydromechanics. **Pisani** (Milan, Reporter for Italy) distinguished between the secreting and excreting functions of the kidney, the latter being mainly the transportation of the urine, after it has been formed, to the outside; it was this function of renal excretion which he discussed. He distinguished between excretory disturbances of motility, particularly with reference to peristalsis, disturbances of tone, and mixed disturbances in which alteration of both these dynamic factors plays a part. These various disturbances may be transitory or permanent and may arise from congenital malformations, from obstructive causes, whether congenital or acquired, from muscular or nerve lesions or any condition which disturbs the patency of the ureteral orifices. Dilatation of the excretory ducts represents the static element only and is often truly compensatory (hypotonic). Hypotonic-hyperkinetic dilatation may give good evacuation whereas hypotonic and nonkinetic dilatation means a permanent change with loss of function.

Rubritius (Vienna, Reporter in collaboration with Fuchs for Hungary) discussed excretion according to the laws of hydromechanics, emphasizing in particular the importance of reabsorption in relation to obstructions and the factor of minute tears in the fornices of minor calyces as balancing the amount of secretion with the amount of excretion. The amount formed in excess by the parenchyma of the kidney can be readily taken back into the circulation by this pyelovenous backflow.

Snapper (Amsterdam, Reporter for Holland) gave a masterly summary of the pathologic physiology of the secretion of the urine with a judicial discussion of the experimental evidence of glomerular and tubular activity, establishing the filtration-reabsorption-secretion theory. He also summarized the nonsecretory functions of the kidney, in which he himself has done considerable work with respect to synthesis of hippuric acid and phenaceturic acid and of the oxidation and formation of am-

monium in the kidney. Of interest is the final paragraph of his summary: "Urine is a supersaturated solution of many substances. Different substances, practically insoluble, are present in solution in the urine in large quantities. This problem is of great importance in the prevention of stone formation. The hydrotropic action of different organic constituents of the urine is discussed. Urea, hippuric, salicylic and mandelic acid and other substances often present in the urine, increase the solubility of calcium salts, especially of Ca oxalate. Besides this direct hydrotropic action, the stabilizing influence of these substances upon the colloids of the urine is of importance in the prevention of stone formation."

A REVIEW OF THE WISCONSIN CANCER INSTITUTE

ALEXANDER BRUNSCHWIG, M.D., CHICAGO, ILL.

(From the Department of Surgery and Division of Roentgenology of the Department of Medicine, University of Chicago)

Under the auspices of the Medical School of the University of Wisconsin and with the financial aid of the Wisconsin Alumni Research Foundation, a Cancer Institute in the form of lectures and round table discussions was held at Madison, Sept. 7, 8, and 9, 1936. On the last day, the meetings were held in conjunction with the State Medical Society. The address of welcome was delivered by President Glenn Frank who expressed his gratification that such a large number of workers in the field of cancer in the United States were present.

The following is a summary of the papers read:

The Influence of Extrinsic Factors in the Development of Induced Tumors in Animals. By Dr. L. Kreyberg, of the University of Oslo, Norway. In genetically controlled strains of mice, skin cancer was induced by tar painting and the effects of certain extrinsic factors on the development of the carcinomas observed. A diet high in magnesium seemed to delay the appearance of skin cancer. No effects were noted by high carbohydrate or fat diets. A liver diet appeared to hasten the development of benign warts but not the subsequent development of carcinomatous degeneration. In animals fed thyroid gland there was a higher incidence of tumors but their appearance was not hastened.

A second paper presented by the author was entitled **The Genetic and Constitutional Aspects of Spontaneous and Induced Tumors.** There is a genetic factor involved in the production of skin carcinomas by application of tar since in genetically pure strains the incidence and time of appearance of these tumors vary. A weak "irritant" in a mouse of strong constitutional susceptibility will produce carcinoma as will a strong "irritant" in an animal of little constitutional susceptibility. Spontaneous carcinoma of the breast in the mouse is in some way associated with ovarian activity since few males develop such tumors. Castration of the females at an early age reduces the incidence of spontaneous breast cancer. An association of breast cancer and ovarian tumors has been noted by the author in his colony of mice. There is no relationship between the susceptibility of a given strain of mice for tar tumors and the incidence of spontaneous mammary cancer.

The Influence of Intrinsic Factors in the Development of Tumors in Mice. By Dr. C. C. Little, Director of the Jackson Laboratory for Cancer Research, Bar Harbor, Maine. To the geneticist, the question of spontaneous tumor formation is a developmental phenomenon similar, perhaps, to the question of morphologic ab-

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normalities. It is not a simple Mendelian heredity because there is for breast cancer, for example, a close sex linkage, and there are linkages with other variable factors, all of which are not inherited. Further investigations are necessary for a clearer conception of the importance of the hereditary factors in the development of spontaneous tumors in these animals.

Familial Occurrence of Cancer. By Dr. Madge T. Macklin, University of Western Ontario, London, Canada. Under existing conditions of the population (in Canada) the laws of probability cannot account for the occurrence of the same types of cancer in related individuals (mother or father, and children). It must be concluded that in cancer in the human race an hereditary factor plays an important rôle. Knowledge of this fact on the part of the laity should lead to earlier medical consultation for symptoms referable to organs which in the individual family histories seem predisposed to malignant neoplasia.

Hormones and the Development of Atypical Growths and Malignant Tumors. By Edgar Allen, Professor of Anatomy, Yale University Medical School, New Haven, Conn. The follicular hormone is not only a powerful stimulant for the proliferation of certain genital epithelia and for the female and male breast, but is also a stimulant for the proliferation of certain mesoblastic tissue. The production of mammary cancer and of spindle cell sarcoma in mice by injections of large quantities of this hormone is of great importance in orienting further investigations of the mechanism of spontaneous malignant tumor formation.

Carcinogenic Substances in the Production of Tumors in Laboratory Animals. By Dr. H. B. Andervont, Biologist, U. S. Public Health Service, Boston, Mass. Some 40 compounds have been synthesized which are capable of inducing carcinoma when applied to the skin or injected into some of the parenchymatous organs, and capable of inducing sarcoma when injected subcutaneously. Among these are 1-2-5-6 dibenzanthracene, 1-2 benzpyrene and methylcholanthrene. Some of the carcinogenic compounds are feebly estrogenic. Isomers of some of them are less potent or innocuous. Simple "irritation" does not appear to be identified with carcinogenicity because some of the innocuous isomers are more irritating than the active compounds themselves. Although the anthracene nucleus is common to most of the substances, it is not indispensable for carcinogenicity. All of the compounds have at least two benzene rings. Methylcholanthrene, one of the most potent agents, may be derived from desoxycholic acid, a constituent of normal bile.

[The work of Kennaway, Hieger, Mayneord, Cook, Dodds, Burrows, and others on the synthesis of carcinogenic compounds constitutes the most important advance in experimental cancer research since the demonstration by Yamagiwa and Itchikawa in 1914, of the carcinogenicity of tar.—A. B.]

Public Lecture: Cancer, a Public Health Problem. By James Ewing, Memorial Hospital, N. Y. Attention was called to the increasing widespread interest in the study of all phases of the cancer problem. The usefulness of surgical treatment, which is becoming more limited in certain respects, is increasing as regards newer operations and in conjunction with irradiation therapy. The latter, from an insecure and minor position, has become a method of prime importance in the curative and palliative treatment of neoplastic disease. Specialization in the treatment of cancer should permit a more efficient clinical attack. There should be several heavily endowed cancer institutes in various parts of the country to lead in the development of more effective treatment and to serve as centers of research in cancer.

The Influence of Wave Length on the Biologic Action of Radiation. By Dr. Gioacchino Failla, Physicist, Memorial Hospital, N. Y. A review of the problems confronting the physicist in making ionization measurements of quantities of irradiation. An original method for such measurements was described. Evi-

dence from the physicist's point of view was presented to show why x-rays and gamma rays of different wave lengths should have different biologic actions. [The latter question, of great practical importance, is by no means settled.—A. B.]

The Reaction of Tissue Cells to Irradiation. By Professor Henri Coutard, of the Radium Institute, Paris, France. If 4,500 r. units of x-radiation measured on the skin are delivered in daily doses of 300 to 400 r. per day to the neck through two opposing lateral portals the epithelium of the mucosa of the faucial regions, palate and pharynx, will be destroyed and the region become covered with a yellowish fibrinous membrane on the thirteenth or fourteenth day from the first exposure. On the twenty-eighth day the cutaneous epithelium will be destroyed and replaced by a similar membrane. Healing of these superficial irradiation ''burns'' is fairly rapid. If the daily dose is 200 r., milder epithelial reactions develop with peaks of intensity every thirteen to fourteen days. If 900 r. are delivered in daily doses to a total of 4,500 r. epithelial reactions do not occur since there is rapid massive necrosis of the underlying connective tissue.

The cardinal principle in the treatment of carcinoma by x-radiation is to deliver the optimal tumor dose (3,600-4,200 r. for nasopharyngeal tumors) in the proper chronology so that epithelial effects are maximum and connective tissue effects are minimum.

When the five-year ''cure'' statistics of 379 patients treated by the daily small dose method were reviewed, it was found that the majority of patients surviving were treated daily for periods of approximately 13 to 14 days, 23 to 26 days, and 38 to 42 days. It is thus suggested that the proper method of x-ray treatment may prove to be the delivery of large doses (2,400 to 3,000 r. surface measurements) in short series of 4 to 8 daily sittings at 13-day intervals for 2 or 3 series to a total surface dose of 6,000 to 8,000 r. Severe local tissue reactions are to be avoided even though this may mean reducing the dose.

[Coutard thus indicates departure from some of the principles previously enunciated by him and which have revolutionized x-ray therapy in the past few years.—A. B.]

Tissue Culture in the Study of Cancer. By Dr. Warren Lewis, Carnegie Institute, Washington, D. C. Moving pictures of normal and malignant cells in culture were exhibited. Ameboid and phagocytic activity, and mitoses were shown in a spectacular manner. Extensive observations indicate that the malignant cell is a permanently altered cell.

The Biology of the Cancer Cell. By Dr. S. P. Reimann, Professor of Experimental Pathology in the Graduate School of the University of Pennsylvania, Philadelphia. A review of experimental studies on the cancer cell. Malignant neoplasia may arise from excess number of cells, ''spare parts,'' occurring in various organs as a result of aberrations in distribution of undifferentiated cells during the early development of the individual organ or tissues.

Filterable Viruses in Malignant Neoplasms. By Dr. J. B. Murphy, Director of Cancer Research, Rockefeller Institute of Medical Research, N. Y. That the filterable principle for the production of fowl sarcoma is actually a ''living virus'' has not been demonstrated. Its true nature remains unknown. A differentiation must be made between agents which actually induce malignant neoplasms and agents which maintain their growth and development. Tar injections may induce sarcomas in fowls, and from these tumors a filterable agent may be obtained which may induce similar tumors in other fowls. This principle is not present in the tissues before the development of tar sarcomas. In papillomas of rabbits induced by the Shope virus, a filterable principle cannot be obtained from the lesion when it becomes malignant.

The Effect of Bacterial Products on the Growth of Malignant Tumors. By Dr. H. B. Andervont, Biologist, U. S. Public Health Service, Boston. Filtrates of meningococci injected into or at a distance from a growing transplantable mouse sarcoma (sarcoma 180) induce an acute hemorrhagic exudate within the tumor which is followed by complete regression. *B. coli* filtrates (purified for the tumor necrosing principle) when injected into or away from growing transplantable mouse sarcoma 37 or sarcomas induced by 1-2-5-6 dibenzanthracene also induce this reaction within three or four hours. Carcinomas are not affected.

The Recognition and Treatment of Early Malignant Lesions of the Uterine Cervix. By Dr. E. Novak, Associate Gynecologist, Johns Hopkins Medical School, Baltimore. A discussion of the methods of early diagnosis of cancer of the cervix and uterus and of the radiologic and surgical treatment.

Treatment of Cancer of the Breast by X-Rays. By Dr. Henri Coutard. Experience has shown that some varieties of breast carcinomas are sufficiently radiosensitive to be permanently controlled by x-ray therapy only. Further clinical investigation may lead to a means of differentiating those best treated primarily by x-radiation, regardless of size, and those best treated by radical operation with or without x-radiation.

On the evening of September 8, 1936, a public meeting was held in the Great Hall of the Memorial Union. An address broadcast by radio, was delivered by Dr. C. C. Little, Director of the American Society for the Control of Cancer, entitled "A Program for the Control and Prevention of Cancer." It was pointed out that cancer accounted for more deaths than any other single pathologic entity. While some forms of cancer are usually in advanced stages when only slight symptoms become manifest, a large percentage of patients with other types of malignant disease may be offered a good opportunity for cure if adequately treated in the early stages which are manifested (breast, uterus, buccopharyngeal cavity, etc.). A plea was made for a change of attitude on the part of the laity, not to regard cancer in secret horror but to face the issue openly. Whereas patients are usually proud to talk with their friends of what appears to them as spectacular recovery from a variety of diseases, the subject of cancer is rarely discussed. Patients who have been cured of cancer should not conceal this fact. The American College of Surgeons has records of over 25,000 cases of cancer controlled for five years or more. The American Society for the Control of Cancer is about to launch a campaign for publicity of cured cases and of the curability of certain of the more common forms when adequately treated in the early stages. This campaign will begin through cooperation with the American Federation of Women's Clubs, and is intended to reach all women in the United States. It is hoped that this will materially increase the number of early curable cases to seek medical advice, and to increase public interest and financial support for study of the disease.

The subjects of the several round table discussions were: Diagnostic Problems, Genetics in Cancer, Filterable Viruses and Cancer, Surgery and Irradiation in the Treatment of Cancer, Cytology of Malignant Neoplasms, and Etiology of Cancer.

The meetings were all well attended; the visitors were made to feel a hearty welcome. Many were permitted to meet personally men with whose writings only they had previously been familiar. The University of Wisconsin, and especially those immediately in charge of the Cancer Institute, are to be highly felicitated for the choice and conduct of the programs, and especially for the *idea* that such a gathering should take place. Now that Wisconsin has shown the way, it is to be hoped that other institutions will emulate the example. Only good can result from such an intimate and direct exchange of ideas and from such a personal contact of those working in the field of cancer.

REPORT OF THE THIRTY-SEVENTH ANNUAL MEETING OF THE AMERICAN ROENTGEN RAY SOCIETY, CLEVELAND, OHIO, SEPTEMBER 29 TO OCTOBER 2, 1936

LEO G. RIGLER, M.D., MINNEAPOLIS, MINN.
(From the Department of Radiology of the University of Minnesota)

THE annual meeting of the American Roentgen Ray Society held in Cleveland, Ohio, September 29 to October 2, 1936, consisted of a large number of papers together with an extensive scientific and technical exhibit. Only the more interesting contributions of this meeting will be reviewed here.

Doctors Howard Hunt, Russell Best, and Frederick Hicken, of Omaha, Nebraska, presented a paper on **The Radiographic Observation of the Biliary Ducts, During and Following Operation, by Cholangiography.** They reported that the biliary tract may be visualized by replacing 20 or 30 c.c. of bile with a nonirritating radiopaque material, such as hippuran, thorotrast or lipiodine by way of the gallbladder or biliary ducts. Immediate radiography at operation gives information regarding calculi in the ducts, strictures, neoplasms, fistulas, cholangiectasis and the patency or occlusion of the biliary ducts which may guide operative procedures. Postoperative visualization is done by injection of radiopaque materials through drainage tubes or external fistulas with demonstration of the above conditions and portrayal of the adequacy of operative and drainage procedures. This method, which has been used for several years, promises to be of great assistance in demonstrating the actual condition of the common duct both during and after operation. The development of a good technic for doing cholangiography in the operating room, as practiced by the authors, may make it possible frequently to avoid drainage of the common duct or to prevent secondary surgical procedures.

Doctors Haig H. Kasabach and Alexander B. Gutman, of New York City, presented a paper on **Osteoporosis Circumscripta of the Skull and Paget's Disease. Fifteen New Cases and a Review of the Literature.** They demonstrated quite clearly that osteoporosis circumscripta is a precursor of Paget's disease or, in a broad sense, an atypical form of Paget's disease. In 32 of the 47 cases which they collected from the literature, including their own cases, osteoporosis circumscripta of the skull was associated with typical Paget's disease somewhere else in the skeleton. In 5 cases in which osteoporosis circumscripta only was found, follow-up studies revealed the development of Paget's disease in or about the areas in the skull within two to eight years.

The classification, pathogenesis, pathology and roentgen features of **Acute Infections of the Mediastinum** were discussed by **Dr. Coleman B. Rabin,** of New York. He pointed out that the majority of suppurative lesions of the mediastinum arise from traumatic penetration of the cervical esophagus and cervical infections. The communication between a mediastinal abscess and its cervical origin may occasionally be demonstrated by injection of iodized oil. The clinical manifestations and surgical treatment of **Acute Infections of the Mediastinum** were presented by **Dr. Harold Neuhof,** of New York. He reported a surprisingly high percentage of recoveries by means of surgical drainage. In the discussion, Dr. Claude Beck, of Cleveland, emphasized the point that many mediastinal infections

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are air-borne and that they are very common in animals; Dr. Alton Ochsner, of New Orleans, called attention to the value of bronchoscopic drainage in the treatment of mediastinal abscess.

A paper on **Roentgen Kymographic Studies of Pulmonary Lesions, by Doctors Wendell Scott and Sherwood Moore,** of St. Louis, dealt with the application of this relatively new method of roentgen study to the movements of the diaphragms, ribs, and mediastinum. By means of kymography the altered motion of these structures under various abnormal conditions such as bronchial stenosis from tumor or foreign body, chronic mediastinitis or pulmonary fibrosis can be graphically demonstrated. While the findings are essentially the same as those demonstrated by fluoroscopy, the kymogram permits a more accurate and permanent recording of motion. In surgical conditions of the thorax this method of study may prove of great value.

The Roentgenological Diagnosis of Pericardial Scars (Adhesive Pericarditis) and Encapsulated Pericardial Effusion was presented by **Dr. Eugene Freedman,** of Cleveland, and discussed by **Dr. Claude Beck.** Freedman described the roentgen findings in the cases which have been operated upon by Dr. Beck and indicated the general results of pericardiectomy (decompression of the heart) as practiced by Dr. Beck. Dr. Beck gave an outline of the indications for surgery in adhesive pericarditis and explained his objection to this term. He also discovered the fallacy of the Brauer operation in the treatment of this condition.

The Physiologic Consideration of Ileus was discussed by **Dr. Alton Ochsner,** who gave it as his opinion that the toxemia and loss of fluids are largely responsible for the fatal results of obstruction. He emphasized strongly the importance of intramural strangulation due to the great distention of the bowel. Ochsner is thoroughly convinced of the crucial value of the roentgenogram of the abdomen in the demonstration of ileus, but he believes that by this method alone adynamic ileus cannot be distinguished from mechanical obstruction.

A paper on **Congenital or Infantile Dislocation of the Hips** was given by **Dr. Edward C. Vogt,** of Boston. He presented evidence to indicate that the dislocation is not present at birth but occurs as a result of relaxation of tendons and ligaments in an otherwise normal joint. **A Clinical and Roentgenological Study of Low Back Pain With Sciatic Radiation** was presented by **Drs. Carl E. Badgley and Fred Jenner Hodges,** of Ann Arbor. They studied 500 cases and found little or no constancy in the roentgenologic findings in the lower spine in these patients. The most common change was a narrowing of the fifth lumbar intervertebral disc.

One of the striking contributions at this meeting was presented by **Drs. Aubrey O. Hampton and J. Maurice Robinson,** of Boston, on **The Lipiodo-Diagnosis of Rupture of the Intervertebral Discs Into the Spinal Canal (With Particular Reference to Those Lesions Simulating Sciatica and Low Back Strain).** They detailed the findings in 40 proved cases of clinically important intraspinal ruptures of the intervertebral discs. The majority of these patients were suffering with intractable pain simulating sacroiliac disease, sciatica, and low back strain. By the injection of iodized oil into the lumbar spinal canal, a characteristic defect in the shadow due to pressure of the displaced nucleus, pulposus can be well demonstrated in the roentgenogram. The surgical relief by removal of this structure was reported.

A symposium on **Adenomas of the Pituitary Body** was presented by **Drs. Elliott C. Cutler and Max T. Schnitker, W. W. Vaughan, and Merrill C. Sosman,** of Boston. Clinical and roentgenologis findings in various types of pituitary tumors were described; the conclusion of both Drs. Cutler and Vaughan was that irradiation should be first attempted in tumors of the pituitary gland before resorting to surgery. It is their experience that about 80 per cent of the chromophobe

and eosinophile adenomas are radiosensitive and probably can be controlled without surgery. The progress of the lesion can be accurately followed by visual field examination. Dr. Sosman pointed out that the basophile adenomas of the pituitary gland are rare as compared with the frequency of the chromophobe and eosinophile adenomas, but their effect upon the individual is much more marked. This tumor causes all of its bizarre and striking effects by hypersecretion and has no local or neighborhood pressure effects. It apparently produces systemic changes through the other endocrine glands. The basophile adenoma is quite sensitive to roentgen ray treatment as judged by the results in three cases which were reported in detail.

A new method of roentgen therapy which has been practiced in Germany since 1931 was described in a paper by **Dr. Eugene P. Pendergrass,** of Philadelphia, entitled **Roentgen Therapy by the Method of Chaoul.** Dr. Chaoul uses a very small, shockproof, fully protected x-ray tube which is brought into close contact with the lesion to be treated. It may be placed in the oral cavity, pharynx, vagina, or rectum if desired. Low voltage is used, and an effect similar to that of surface applications of radium is produced. It is being used in Germany as a substitute largely because of the inability of the Germans to purchase radium.

Doctors Ira I. Kaplan and Sidney Rubenfeld, of New York, presented a paper on **Prolonged Low Intensity Irradiation.** The authors devised a bedside x-ray therapy unit, constructed along shockproof lines, which would permit them to give, economically and safely, prolonged low intensity x-ray therapy treatments with the patient comfortably cared for in his own bed. The machine is operated at a relatively low voltage, 110 KV, with only 1 MA of current, and the filter employed is ⅛ to ¼ mm. of copper plus 1 mm. of aluminum, treatment being given at a distance of 50 to 80 centimeters. The authors have treated a wide variety of cases in this manner; infectious processes, particularly, such as bronchiectasis, unresolved pneumonia, and psoriasis, were first attempted. Then leucemias and lymphogranulomas were added, and now the authors are studying the effects of this type of irradiation on malignant tumors. They have obtained some encouraging results in certain cases. By combining the principle of protracted fractional irradiation together with a modified continuous irradiation, they believe that they are presenting a new type of therapy which merits further study.

A paper on **Fracture of the Femoral Neck Following Irradiation, by Doctors Harold W. Jacox, Robert G. Dalby, and Norman F. Miller,** of Ann Arbor, detailed a series of 14 cases in whom spontaneous fracture of the femoral neck occurred following irradiation of the pelvis for gynecologic conditions. The exact cause was not apparent, but careful histologic studies in two cases revealed no evidence of metastasis.

Dr. Richard Dresser, of Boston, presented a paper on **The Production of Super Voltage Roentgen Rays by Means of the Van de Graaff Generator.** He described a method for the production of high voltage roentgen rays by a relatively simple apparatus. This consists of a high voltage body mounted on an insulator which is charged by means of electrons carried by belts running at high speed. An x-ray tube of the cascade type under continuous exhaustion is energized from this high voltage body, and small quantities of very high voltage x-rays may thus be produced.

Dr. Robert B. Taft, of Charleston, presented studies **Concerning the Radioactivity of Thorotrast by the Use of the Geiger Counter.** He found that 75 c.c. of the commercial preparation thorotrast gave a count equivalent to the gamma radiation of 1.37 micrograms of radium. This is in contrast with the failure to detect any radioactivity by the simple procedure of placing the thorotrast on an x-ray film.

Two outstanding technical achievements were presented on the last day of the meeting. The first paper was entitled **Planigraphy and Tomography: The Roentgenographic Representation of Plane Sections of Solid Objects, by Dr. Robert Andrews,** of Cleveland. In this presentation there was shown, for the first time in this country, a new method of roentgenography with which many experiments have already been conducted abroad. The purpose of this procedure is to project images of predetermined plane sections of solid objects on a roentgen film, with sharpness, while the structures in a different plane of the same object are blurred and indistinct. This is accomplished by moving the roentgen ray tube in one direction while the film is moved simultaneously in the opposite direction during the exposure, the object remaining fixed. The tube and film move around a point which is fixed at the level of the desired plane. A simple example of this procedure is the roentgenography of the sphenoid sinus. By correct application of this principle, an anteroposterior projection of the skull may be obtained in which the sphenoid sinus stands out from its surroundings as a clear-cut sharp image, while the remaining structures of the skull are blurred and indistinct. The practical value of this innovation is still doubtful.

The second paper, **A Preliminary Report on Cine-Fluorography,** was one of the more important achievements of the meeting. This was presented by **Drs. William H. Stewart, William J. Hoffman, and F. H. Ghiselin,** of New York. By the use of a special lens, a very sensitive motion picture film, a highly sensitive fluoroscopic screen, and the application of heavy exposures, the authors have produced, for the first time, a very satisfactory motion picture made directly from the fluoroscopic image. The results were particularly good in the visualization of the thorax, although intraabdominal structures were also demonstrated. It is possible that the method will be of value chiefly for experimental research and teaching. At present the expense of the equipment and the excessive exposures make it impractical to use for diagnostic purposes. For study and teaching, particularly of diseases of the thorax, such motion picture films will no doubt be exceedingly useful.

RÉSUMÉ OF THE MEETINGS OF THE ASSOCIATED ANESTHETISTS' SOCIETIES AT THE FIFTEENTH ANNUAL CONGRESS OF ANESTHETISTS, PHILADELPHIA, OCTOBER 19 TO 23, 1936

EDWARD B. TUOHY, M.D., ROCHESTER, MINN.
(From the Mayo Clinic)

THIS past meeting was one of the largest assemblies of the Congress of Anesthetists. It was held in conjunction with the American College of Surgeons, and its representation included several renowned personages from the United States, Canada and abroad. The meeting was appropriately dedicated to the memory of the late Dr. E. I. McKesson.

The various scientific sessions dealt with practically all phases of anesthesia, emphasizing current research in anesthesia and analgesia and the newer methods of administering anesthetic agents. Interspersed among presentations at the general assemblies were various clinics at some of the local hospitals which dealt with the administration of anesthetic agents.

The University of Pennsylvania School of Medicine and Surgical Research had several demonstrations, under the direction of Dr. I. S. Ravdin and his associates. Both Dr. Ravdin and Dr. Goldschmidt gave presentations on the use of divinyl ether, and gave both clinical and experimental data relative to its usefulness as one of the new anesthetic agents. In brief, it was their opinion that divinyl ether should be used for operations which do not require more than an hour's time, and they emphasized the more conservative use of this agent for operations lasting up to a half hour. They have demonstrated experimentally that damage to the liver may result with too prolonged use or too rapid administration of divinyl ether.

Spinal anesthesia was discussed at some length by various investigators, as was also the use of several agents for producing it. Professor Trempe, of Quebec, advocated the use of nupercaine for spinal anesthesia, according to the method of Howard Jones, and this method and agent for producing spinal anesthesia were approved of by several other workers. There were numerous discussions, however, regarding the use of other types of agents, such as procaine, metycaine, and pantocaine. There is apparently no unanimity of opinion as to which agent or technic seems to be the most practical and valuable, since various agents in the hands of certain investigators seem to be satisfactory; and likewise, various modifications of spinal technic seem to be satisfactory in the hands of certain individual workers.

Epidural anesthesia was discussed by Dr. A. L. Soresi, of New York, and its usefulness as an added method of regional anesthesia commented on, especially for operations on patients who are more or less debilitated. Epidural anesthesia causes much less fall in blood pressure and is practically devoid of the complication of lumbar puncture headache. Undoubtedly epidural anesthesia will be used more and more frequently as the technic is mastered by more individuals. The secret of its use lies in the fact that the epidural space has a negative pressure, which can be measured by means of a simple manometer attached to the needle or by means of the so-called hanging drop technic of Dr. Soresi.

Cyclopropane anesthesia was quite thoroughly discussed by Dr. Harold Griffith, of Montreal, and by Dr. Eversole, of Boston. It was the current opinion that cyclo-

propane is a very useful anesthetic agent, but that very definite care must be exercised in its administration, since it is a very potent agent, especially in its effect on respiratory and cardiac function.

The intratracheal method of anesthesia was presented in detail by Dr. Sykes and Dr. John Hunter and others, and they emphasized the point that it provides an adequate airway for to-and-fro respiration and furnishes improved surgical relaxation. Numerous new devices for introducing intratracheal tubes blindly through the mouth were shown, and also several other ingenious instruments for the administration of intratracheal anesthetics.

Intravenous anesthesia by means of some of the barbiturates was likewise discussed, and such agents as evipal soluble, pentothal sodium, and methylnumal were submitted as useful agents in producing anesthesia of short duration by the intravenous route. The essential feature in the administration of barbiturates is that the agent must be administered very slowly and intermittently, and not according to body weight. The use of these agents should be limited to operations of short duration which do not require maximal muscular relaxation.

A report of 5,000 administrations of avertin for rectal anesthesia was made by Dr. L. B. Mueller, of Indianapolis. This is one of the largest series of cases in which avertin has been used, and it is quite striking on the basis of the large number of cases apparently without untoward results.

Dr. Brian Sword, of New Haven, presented a method of continuous gas and air analgesia for obstetric cases. The essential feature of this particular type of analgesia is that the patient is kept in a very mild state of anesthesia throughout the course of the first stage of labor. Technically the success of the method depends on having the aperture for the entrance of the anesthetic agent close to the patient's face and not near the intake for air at the top of the face mask. The advantage of this type of analgesia is that the patient can assist in labor, and at the same time the severity of the pains during labor are minimized. As labor progresses, the depth of anesthesia may be increased as is deemed necessary.

The use of cyclopropane in obstetric practice has proved quite satisfactory, and one worker stated that there was less uterine hemorrhage after the use of cyclopropane and less postoperative distention.

Several restorative or analeptic drugs were studied by Dr. E. A. Rovenstine, of New York, and in his opinion, coramine, picrotoxin, and metrazol were all suitable agents in the various types of cases studied. Any one of these particular drugs, if given in large enough quantities, will produce convulsions, but when given in therapeutic dosages they are stimulating in their action.

Complete papers covering these numerous phases of anesthesia will be published subsequently in the ensuing issues of *Current Researches in Anesthesia and Analgesia*, and anyone interested may secure the added information from that source.

RÉSUMÉ OF THE MEETING OF THE AMERICAN SOCIETY OF ANESTHETISTS AT THE ACADEMY OF MEDICINE NEW YORK, N. Y., OCTOBER 8, 1936

EDWARD B. TUOHY, M.D., ROCHESTER, MINN.
(From the Mayo Clinic)

DR. MILTON PETERSON, of Bellevue Hospital, presented a report on the technic for endobronchial anesthesia. The use of the direct laryngoscope* is essential, since the technic involves the passing of a curved rubber tube into the trachea and between the vocal cords, under direct vision. It is necessary that the patient be relaxed under surgical anesthesia before this maneuver is attempted; otherwise, unnecessary trauma to the region of the glottis may occur. The usual methods of induction are used, and nitrous oxide and ether vapor, or cyclopropane, are used as anesthetic agents. After the tube has been successfully directed into the trachea, it is advanced until resistance is felt, indicating that the tip of the endotracheal tube is at the bifurcation of the trachea. The direction in which the tip of the tube is rotated determines largely into which bronchus the endotracheal tube has entered. Usually, little resistance is encountered in passing the tube into either main bronchus. An inflatable rubber cuff of the Waters-Guedel type surrounds the endobronchial tube about an inch (2.5 cm.) from its distal end, so that, when intubation of the bronchus has been successfully carried out, a comparatively airtight circuit may be obtained by inflating the cuff. The cuff is inflated with air by means of a small syringe which is adapted to a small catheter attached to the large endobronchial tube. It was further suggested that the inflatable cuff would aid also in preventing secretions from the opposite bronchus from entering the lung to which the anesthetic is being administered. For the maintenance of anesthesia, the free end of the tube, as it emerges from the mouth, is connected by means of special adapters to the leads of a standard gas machine, and any of the usual anesthetic agents may be given through this endobronchial tube.

Dr. Van Gilluwe presented a motion picture of the carbon dioxide absorption technic and the use of cyclopropane for special surgical operations. He also described his method of intratracheal and endobronchial intubation by means of soft rubber tubing of the Magill type. In addition, he presented an ingenious demonstration which showed the passage of an intratracheal tube through an artificially constructed trachea and bronchial tree. Sections of rubber tubing of approximately the diameter and size of adult tracheal rings were joined together with transparent windows between the rubber rings, which permitted direct observation of the intratracheal tube as it was advanced into the trachea and main bronchi. The usual type of tube used for intratracheal or endobronchial anesthesia is made of soft rubber and possesses a natural curve so that it may be easily introduced, when greased with sterile petrolatum, through the nose and thence into the trachea. It may also be introduced orally under direct vision with a laryngoscope. The Magill intratracheal tubes are supplied in various sizes for children and adults. The average tube for an adult is approximately 26 cm. in length and 1.3 cm. in outside diameter. This particular size of tube will permit easy to-and-fro respira-

*A modified laryngobronchoscope, which permits direct vision in the region of the bifurcation of the trachea, is used by some workers. This instrument aids in passing the endobronchial tube into whichever main bronchus is to be used.

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tion to occur within the tube, and will serve as a good airway in case artificial respiration is necessary. Intratracheal tubes and endobronchial tubes are also available with inflatable rubber cuffs at the distal end if so desired.

Dr. Sidney Wiggin, of Boston, considered the use of pontocaine (pantocain) and procaine in spinal anesthesia. In his experience, the administration of pontocaine alone has not given a complete sensory anesthesia in all cases, although motor paralysis was satisfactory. However, he has found that a combination of pontocaine and procaine has given satisfactory sensory anesthesia and adequate relaxation. In the 700 cases studied, in which pontocaine and procaine were administered as spinal anesthetics, he observed less nausea and less variation in blood pressure than when either procaine or pontocaine was used alone. Pontocaine is approximately ten times more potent than procaine and is noted for its prolonged action. The combination of about 60 per cent pontocaine and 40 per cent procaine has been a satisfactory mixture. For example, 6 mg. of pontocaine and 40 mg. of procaine would be the usual proportion for a dose of 100 mg. The patients to whom this mixture of spinal anesthetics was administered were carefully selected, and debilitated patients were omitted. As a means of determining the contraindication to spinal anesthesia in these studies, ephedrine sulphate was administered in doses of 50 mg. in order to ascertain the individual's response to the pressor agent. If 50 mg. of ephedrine sulphate did not raise blood pressure and improve the pulse of the individual under study within fifteen minutes, the spinal anesthetic was not used. The author routinely used the second and the third lumbar interspace as the site of injection and emphasized that the rate of injection of the anesthetic should not exceed 0.5 c.c. per second. He also has devised a special dilution table which he uses as a general guide in determining the doses and dilutions of the anesthetic for various types of operation. All of his patients received preliminary medication prior to spinal anesthesia, which generally consisted of 1½ grain (0.097 gm.) of pentobarbital sodium, ¼ grain (0.016 gm.) of morphine sulphate, and $\frac{1}{150}$ grain (0.0004 gm.) of scopolamine. In a few cases, nitrous oxide and oxygen was used to supplement the spinal anesthesia. Postoperatively, unless there were contraindications, the patients were moved in bed from side to side frequently in order to prevent pulmonary disturbances. The usual intravenous and rectal methods were used for supplying fluids immediately after operation. Either a 5 per cent solution of dextrose or a physiologic saline solution was given. He concluded that the mixture of pontocaine and procaine was more satisfactory than either preparation used separately, from the standpoints of nausea, vomiting, respiratory depression, and variations in blood pressure.

Book Reviews

Recent Advances in Genitourinary Surgery. By H. Bailey and N. M. Matheson. Cloth. Pp. 205, with illustrations. Philadelphia and London, 1936, P. Blakiston's Son & Company.

This book better could be called "Current Practices in Urology," since it deals with many matters which are not, strictly speaking, recent advances. The reviewer assumes that it is intended to make available to the general practitioner and general surgeon the current trends in urology. Viewed in this light, it is a very valuable little volume, since it is concise, pointed, and contains a useful bibliography. Its value in this field would be much increased by the inclusion of critical comments from the authors. As it stands, it quotes in places conclusions of somewhat doubtful validity, particularly as concerns the proved value of certain recently developed operations, which certainly merit critical comment.

As a review of current literature for urologists, it is a little too brief to be compared with the "Yearbook of Urology."

The chapter on excretory urography is excellent, presenting clearly the indications, limitations, and value of the method. Particularly important is the emphasis upon its limitations in discovering small foci of tuberculosis, and upon the resultant indications for retrograde pyelography.

The view of the value of decapsulation in nephritis is unusually hopeful, and is one not generally held; many will question the notion that nephropexy is required whenever the renal pelvis sinks below the fourth lumbar vertebra.

The review of the present treatment of infections in the urinary tract is unusually complete, although the value of neoarsphenamine in chronic coccal infections is deserving of mention, and the ketogenic diet receives less space than it appears to deserve. The value of drainage by ureteral catheter or nephrostomy is emphasized.

The growing enthusiasm for conservative operations in hydronephrosis from obstruction at the ureteropelvic junction is reflected in this discussion. One would like to see the Schwyzer-Foley operation mentioned.

The section on urinary calculi contains an excellent presentation of current views of their etiology; the emphasis on the value of nephrostomy after the removal of renal stones is sound.

The newly developing operations upon the sympathetic innervation of the urinary tract are well discussed, although the views of the Harrises as to the importance of disturbances of sympathetic innervation in causing renal pain are not yet widely accepted. Presacral neurectomy is explained.

The reviewer was a little startled to find, in a work entitled "Recent Advances," a discussion of the dangers of sudden emptying of the bladder together with a recommendation for recompression when the bladder is inadvertently emptied. This problem was mentioned in the Ebers Papyrus, and was frequently discussed at the beginning of the nineteenth century. The theory was revived at the beginning of this century, but its validity has never been proved. The persistence of this idea is regrettable, since it tends to cause the surgeon to blame nature for the disasters which often follow his introduction of bacteria into the distended bladder, and to delay acceptance of Bumpus' idea that it is the maintenance of rigid asepsis in catheterization, rather than the rate of emptying, which is important.

There is an admirable summary of the status of the therapy of tumors of the bladder, and the authors' attitude toward transurethral resection of the prostate is unusually free from bias. Their conclusion that relatively large lateral lobes require prostatectomy will be disputed only by those of large experience with resection.

Many skeptics will be pleased by their reference to ureteral stricture as "this somewhat nebulous lesion." The more widely used methods of transplantation of the ureter into the bowel are described.

The chapter on the surgery of the adrenal quotes too many indications and omits to mention the very real danger of fatal postoperative adrenal insufficiency, a danger which will not disappear until it is possible to determine preoperatively whether both adrenals are present and functioning. The current work in the United States on adrenalectomy in hypertension is not mentioned.

The recent observations on the occurrence of the hormones of pregnancy in the urine in teratoma testis is well described, as is the injection treatment of hydrocele and varicocele.

There are also discussions of renal function tests, treatment of uremia, renal cysts and neoplasms, urogenital tuberculosis, retention and incontinence of urine, and sterility; but the data presented do not really belong to recent advances.

One may summarize by saying that here is a concise, excellent volume for the general practitioner or surgeon interested in keeping abreast of current practices, and lacking only a more critical attitude on the part of the authors.

Books Received

The receipt of books is acknowledged in this section and this statement must be regarded as sufficient acknowledgment of the courtesy of the sender. Selections will be made for more extensive review dictated by the interests of our readers and as space permits.

DISEASES OF THE CORONARY ARTERIES AND CARDIAC PAIN. By Robert L. Levy, Columbia University, New York. Cloth. Price $6. New York, 1936, The Macmillan Company.

NEUROLOGICAL SURGERY. By Loyal Davis, Northwestern University Medical School, Chicago. Cloth. Price $6. Pp. 429, with 172 engravings, 2 plates. Philadelphia, 1936, Lea & Febiger.

A TEXTBOOK OF SURGERY. By Frederick Christopher, Northwestern University Medical School, Chicago. Cloth. Price $10. Pp. 1608 with 1349 illustrations. Philadelphia, 1936, W. B. Saunders Company.

MINOR SURGERY. By Frederick Christopher, Northwestern University Medical School, Chicago. Cloth. Price $10. Third edition. Philadelphia, 1936, W. B. Saunders Company.

AMERICAN CHAMBER OF HORRORS. By Ruth DeForest Lamb. Cloth. Price $2.50. Pp. 418. Second edition. New York, 1935, Farrar & Rinehart.

MODERN MOTHERHOOD. By Claude Edwin Heaton, New York University College of Medicine. With Introduction by Hazel Corbin. Cloth. Price $2.00. Pp. 271. New York, 1935, Farrar & Rinehart.